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Predictors of Psychosis Remission in Psychotic Disorders That Co-occur With Substance Use

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Objective: **To examine rates and predictors of psychosis remission at 1-year follow-up for emergency admissions diagnosed with primary psychotic disorders and substance-induced psychoses.** ***Method:*** **A total of 319 patients with comorbid psychosis and substance use, representing 83% of the original referred sample, were rediagnosed at 1 year postintake employing a research diagnostic assessment. Remission of psychosis was defined as the absence of positive and negative symptoms for at least 6 months. Likelihood ratio chi-square tests and multivariate logistic regression were the main means of analysis.** ***Results:*** **Of those with a baseline diagnosis of primary psychotic disorder, 50% were in remission at 1 year postintake, while of those with a baseline diagnosis of substance-induced psychosis, 77% were in remission at this time point. Lower Positive and Negative Syndrome Scale (PANSS) symptom levels at baseline, better premorbid functioning, greater insight into psychosis, and a shorter duration of untreated psychosis predicted remission at 1 year in both diagnostic groups. No interaction effects of baseline predictors and diagnosis type were observed. A stepwise multivariate logistic regression holding baseline diagnosis constant revealed the duration of untreated psychosis (odds ratio [OR] = 0.97; 95% confidence interval [CI] = 0.95, 0.997), total PANSS score (OR = 0.98; 95% CI = 0.97, 0.987), Premorbid Adjustment Scale score (OR = 0.13; 95% CI = 0.02, 0.88), and Scale to Assess Unawareness of Mental Disorders unawareness score (OR = 0.84; 95% CI = 0.71, 0.993) as key predictors of psychosis remission.** ***Conclusions:*** **The association of better premorbid adjustment, a shorter duration of untreated psychosis, better insight into psychotic symptoms, and lower severity of psychotic symptoms with improved clinical outcome, reported previously in studies of schizophrenia, generalizes to psychosis remission in psychotic disorders that are substance induced.**

Key words: primary psychosis/substance-induced psychosis/outcome

Introduction

Psychotic disorders that co-occur with substance use include both primary psychotic disorders, such as schizophrenia, and substance-induced psychotic disorders. Little is known, however, about the life course of psychosis when it is accompanied by substance use.[1] In persons with primary psychotic disorders such as schizophrenia, substance abuse is widespread[2–5] even at the time of the first onset of psychosis.[6] Numerous negative outcomes, such as more frequent use of the hospital,[7,8] more frequent suicide attempts,[9,10] violent behavior,[11] and residential instability and homelessness,[12,13] have been reported. Although the rate of substance-induced psychosis among people with substance-use disorders is not known, clinical reports also link substance-induced psychosis to the need for hospitalization, violent behavior, suicidality, and arrests.[14] It is possible that substance-induced psychoses, like primary psychoses, can be chronic and disabling.[15] However, a comparison of the outcome of primary psychoses and substance-induced psychotic disorders has been limited by the absence of longitudinal data on carefully diagnosed patient samples. A greater understanding of illness course and outcome in all types of psychotic disorders that co-occur with substance use is important for both treatment and prevention.

Outcome in schizophrenia and other psychotic disorders has been examined in numerous studies by measuring symptom remission, social functioning, and utilization of mental health services, including hospitalization.[16–18] The interrelationship of these various dimensions of outcome in psychotic disorders that co-occur with the use of drugs or alcohol is not well documented. Predictors of outcome

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in schizophrenia and other primary psychotic disorders have been studied extensively. Female gender,[19–21] good premorbid functioning,[16,17,22] insight into psychosis,[23] and a shorter duration of untreated psychosis[18,24–27] have all been associated with improved outcome, variously defined. These factors and other possible predictors of outcome have not been studied in patients with comorbid psychosis and substance use, enabling comparisons of primary psychotic disorders and substance-induced psychoses. Although substance use has been linked to a worse overall outcome in schizophrenia and other primary psychotic disorders, it is not known whether comorbid substance-use disorders are of greater or lesser significance for outcome than the other predictors noted above.

We have reported previously on differences between early-phase primary psychotic disorders that co-occur with substance use and substance-induced psychoses observed in a cohort of 386 patients at admission to upper Manhattan psychiatric emergency departments.[28] A comparison of substance-induced psychoses with primary psychotic disorders diagnosed at the baseline assessment found that substance-induced psychoses were associated with greater substance dependence, parental substance abuse, and visual hallucinations, while primary psychotic disorders were characterized by greater symptom severity. This article, based on a 1-year follow-up of this cohort, is focused on the nature of psychosis remission in substance-induced psychosis compared with primary psychosis. The aims of this phase of the investigation were (1) to describe remission of psychosis in the primary psychotic disorder and substance-induced psychosis groups at 1 year postintake; (2) to study the main effects of demographic characteristics, premorbid social adjustment, insight into psychosis, duration of untreated psychosis, and clinical characteristics assessed at intake on remission; (3) to study the interaction of baseline predictors with diagnosis type on psychosis remission; and (4) to determine the key predictors of psychosis remission controlling for type of psychosis diagnosis at 1 year. Although the literature on schizophrenia strongly implicates both demographic and clinical factors as important predictors of outcome in primary psychotic disorders, we did not assume that any or all of them would also predict psychosis remission in the substance-induced psychosis group.

Research Methods

Overview

Research methods including the specific diagnoses included in the primary and substance-induced categories have been presented in detail elsewhere[28] and are described only briefly here. The study sought to identify patients experiencing psychosis in an early phase. We followed the precedent established in prior research on early psychosis[16] by excluding those whose first hospitalization for psychosis occurred more than 6 months prior to the index admission. We did not include individuals who had experienced an extended duration of continuous psychotic symptoms in the absence of prior treatment. Study patients were recruited from 5 psychiatric emergency departments in upper Manhattan. They were English or Spanish speaking, were between the ages of 17 and 45 years, had at least one psychotic symptom assessed during administration of the baseline research protocol, and had used alcohol and/or drugs within the past 30 days. Study patients were interviewed at baseline after voluntary informed consent was obtained. They were contacted monthly to obtain information on clinical status and service use and were reinterviewed in depth at 6 and 12 months by masters' level interviewers trained in the administration of study instruments.

There was no attempt to control treatment rendered during the crisis episode or upon follow-up; rather, treatment was "usual care" provided by clinicians in the service systems from which patients were recruited. In a naturalistic investigation such as this, treatment can be confounded with illness course (eg, treatment received may reflect illness course rather than treatment received influencing outcome), obviating the ability to make clear inferences on the effect of treatment on remission outcome. Therefore, study of the effect of treatment was not a goal of this investigation. The research protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute/Columbia University Medical Center and the other institutions from which study patients were recruited.

Of the 386 patients meeting Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for either primary psychotic disorder or substance-induced psychosis at baseline, follow-up data were obtained on 319 (83%). Sixty-seven patients (17%) were not interviewed postbaseline. Thirty-one patients were lost to follow-up, 16 left the region and could not be interviewed, 11 were incarcerated and could not be interviewed, 8 refused to continue their participation in the study, and 1 died. When the 67 patients not interviewed postbaseline were compared with the interviewed group, the not-interviewed group had greater homelessness, unemployment, and poorer family support. There were no differences in gender, age, race, level of education, jail or prison history, or baseline diagnosis of primary or substance-induced psychosis.

Research Diagnostic Assessment

Research diagnostic assessments at baseline and at the 1-year follow-up were made using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM).[29] Details of PRISM/DSM-IV instrument and its procedures for the implementation of DSM-IV criteria for psychotic disorders have been described previously.

The baseline PRISM/DSM-IV diagnosis of the primary psychotic disorder–substance-induced psychotic disorder distinction was used in the analyses reported in this article. The multiple data sources for the PRISM included patient self-reports obtained during the interview, observations and diagnostic assessments of clinical staff, hospital charts, family/collateral reports of patterns of substance use and onset/offset of psychosis, and urine toxicology screens conducted routinely as part of the follow-up interview procedures.

The test-retest reliability of the PRISM/DSM-IV psychiatric diagnoses in substance-abusing patients has been reported elsewhere.[29,30] Reliability of PRISM diagnoses relevant to this report in 285 patients in substance-abuse/dual diagnosis/mental health settings was good to excellent for current and lifetime primary and substance-induced psychosis and schizophrenia (k = 0.59–0.86) and for current and lifetime alcohol, cannabis, cocaine, and heroin dependence (k = 0.63–0.96).[30] The validity of a Spanish version of the PRISM has been studied in relation to the Longitudinal, Expert, All Data (LEAD) standard.[31] In that study, the PRISM/LEAD concordance was excellent to good (any current psychotic disorder, k = 0.85; past substance-induced psychotic disorder, k = 0.68). PRISM diagnostic assessments are based on computer-generated diagnostic algorithms applying DSM-IV criteria.

Remission: The Outcome Variable

Remission of psychosis, the chief outcome variable, is based on 1-year PRISM data. The PRISM defines *remission* as the absence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (affective flattening, alogia, avolition) for a period of at least 6 months prior to the interview, which in this case was at the 1-year follow-up. This definition corresponds to full remission in DSM-IV.

Baseline Predictors of Outcome

The PRISM interview was the source of information for the diagnosis of substance dependence. In this report, we focus on the diagnosis of abuse/dependence on *any* type of drug, including alcohol. Primary psychosis cases included any type of nonaffective or affective psychosis. Cannabis, alcohol, and cocaine were the most common substances involved in substance-induced psychosis; however, 2 or more substances were involved in nearly 40% of cases. Cannabis and alcohol were the most common substances used by primary psychosis patients.

The subject's self-report of the number of days (weeks, months) prior to the baseline interview that a psychotic symptom was first experienced was elicited during the PRISM interview. Most patients had received little or no treatment for psychosis prior to the baseline episode. We defined *duration of untreated psychosis* as the number of days from the first psychotic symptom reported in the PRISM interview to the index admission at baseline. Days were converted to months for the analysis reported here.

Demographic data and information on education and employment were obtained using the Community Care Schedule.[32] Psychiatric symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).[33] This instrument yields a total score on overall psychopathology (total PANSS) and has subscales yielding data on the positive symptoms of psychosis, negative symptoms, and overall general psychopathology. The total PANSS score is a composite of the individual scale scores. The alpha coefficients of reliability for the PANSS scores are as follows: positive scale = .78, negative scale = .81, and general psychopathology scale = .78. Symptoms experienced in the 7-day period prior to the assessment are considered in determining PANSS ratings, which are made on 7-point scales ranging from none (1) to severe (7). The PANSS interview was the first assessment administered in implementing the study protocol at baseline in order to capture the subject's clinical status at admission to the emergency department. In 61% of cases, the PANSS assessment was completed within the 7-day window. The most common reason for a delayed PANSS assessment was that the subject was too ill to undergo voluntary informed consent procedures. There were no differences in the relationship of total PANSS scores to diagnostic classification between assessments made within 7 days compared with those made more than 7 days after admission to the emergency department.

Psychosocial, educational, and occupational functioning in childhood, adolescence, and adulthood were rated with the Premorbid Adjustment Scale (PAS).[34] The alpha coefficient of reliability for the PAS was .87. The Scale to Assess Unawareness of Mental Disorders (SUMD)[35] was used to evaluate an individual's insight into having a mental illness. The instrument yields 2 scores: the unawareness of symptom score (alpha = .68) and the misattribution for symptoms score (alpha = .63). The former assesses the awareness of the existence of a psychotic symptom, and the latter assesses the individual's understanding that a psychotic symptom is a manifestation of a mental illness. Patients were given perfect scores on attribution for responses that indicated the individual knew that the symptom being rated was either due to a mental illness or caused by the use of a substance (eg, "I saw a vision because of the PCP I smoked"). Near-perfect scores were also given for responses such as "my mind is playing tricks on me," "chemical imbalance," or "nervous breakdown." There was no requirement that the attribution had to match the PRISM/DSM-IV diagnosis for that patient.

Table 1. The Relationship of Demographic Characteristics to Remission at 1 Year

Demographic Characteristics	Remission at 1 Year Follow-up		OR (95% CI)	Statistical Test: LRT (1 df)
	No = 124	Yes = 195		
Gender (%)				
Male	44.1	55.9	0.74 (0.45, 1.20)	1.50
Female	36.7	63.3		
Employment (%)				
No	41.5	58.5	1.76 (0.97, 3.16)	3.51
Yes	28.8	71.2		
Race (%)				
Black	41.5	58.5	1.23 (0.78, 1.93)	0.77
Hispanic/others	36.7	63.3		
Level of education (%)				
No high school diploma	39.5	60.5	1.05 (0.67, 1.64)	0.04
High school or more	38.4	61.6		
Age				
Mean	27.75	28.82	1.02 (0.99, 1.04)	1.21
SD	8.13	8.58		

Note: df, degrees of freedom; SD, standard deviation.
*$P < .05$; **$P < .01$; absence of * or ** indicates nonsignificance.

Statistical Methods of Analysis

We used logistic regression to predict remission of psychosis at 1 year as a function of baseline diagnostic status, demographic variables, and baseline clinical variables. A series of models were developed that varied in complexity. The first set documented bivariate associations of remission with each of the potential explanatory variables. The second set examined demographic and clinical variables in models that adjusted for diagnosis (substance induced vs primary psychosis). This set established which explanatory variables contributed directly to the prediction of remission above and beyond diagnosis. The third set examined interactions of baseline clinical predictors with diagnosis type, in order to determine if the importance of each predictor varied within diagnostic type. In a final set, we included multiple explanatory variables at once to determine which variables were most potent predictors of remission. These variables are the ones that are most likely to add new information to clinicians who are assessing the likelihood of remission among patients presenting with both psychotic and substance-related symptoms. All statistical tests are reported using likelihood ratio chi-square tests (LRTs) from the logistic regression analyses.[36]

Findings

Remission of Psychosis at 1 Year

At the 1-year follow-up, 61% of the study's 319 patients were in remission. They were disproportionately from the group with a baseline diagnosis of substance-induced psychosis. In all, 77% of the 133 patients in this group were in remission at 1 year, whereas only 50% of the 186 patients with a baseline diagnosis of primary psychosis were in remission at this time point (odds ratio [OR] = 3.29; 95% confidence interval [CI] = 2.01, 5.39; LRT [1] = 24.01, $P < .01$).

Baseline Predictors of Remission Outcome

Demographic characteristics of study patients are shown in table 1. OR and LRTs show no significant relationships for the effect of any demographic characteristic and remission.

Table 2 shows the relationship of baseline clinical variables to remission at 1 year, adjusting for diagnosis type. Findings indicate that a shorter duration of untreated psychosis is related to psychosis remission at 1 year (LRT [1 df] = 14.95, $P < .01$). For each additional month that psychosis was untreated, the odds of remission at 1 year are reduced by a factor of 0.97. Lower PAS scores, indicating better adjustment, are related to psychosis remission (LRT [1 df] = 12.92, $P < .01$). A lower total PANSS baseline score, indicating less severe symptoms at the initial assessment, was related to remission of psychosis at this time point (LRT [1 df] = 17.89, $P < .01$). Lower SUMD unawareness of symptom scores, indicating greater awareness of psychotic symptoms at the initial assessment, were related to remission at 1 year (LRT [1 df] = 11.33, $P < .01$). Similarly, lower SUMD misattribution of symptom scores, indicating greater awareness at the initial assessment that a psychotic symptom was due to illness, were related to psychosis remission

Table 2. Relationship of Baseline Clinical Variables to Remission at 1 Year

Baseline Predictors	Remission at 1 Year Follow-up		Adjusted[a] OR (95% CI)	Statistical Test Adjusted[a] LRT (1 df)
	No = 124	Yes = 195		
Duration of untreated psychosis in months				
Mean	16.13	9.01	0.97 (0.95, 0.98)	14.95**
SD	14.68	12.57		
PAS score				
Mean	0.36	0.30	0.04 (0.01, 0.23)	12.92**
SD	0.15	0.13		
Total PANSS score				
Mean	69.60	57.18	0.97 (0.96, 0.99)	17.89**
SD	20.70	17.29		
Unawareness of symptom score				
Mean	2.97	2.13	0.78 (0.67, 0.90)	11.33**
SD	1.40	1.78		
Misattributions of symptom score				
Mean	3.30	2.33	0.78 (0.68, 0.89)	14.21**
SD	1.66	1.99		
Drug dependence (%)				
No	38.5%	61.5%	0.60 (0.35, 1.02)	3.52
Yes	39.0%	61.0%		

Note: df, degrees of freedom, SD, standard deviation.
[a]Adjusted for diagnostic type (primary psychosis vs substance induced): logistic regression analysis with 2 main effects (one predictor and diagnosis type).
*$P < .05$; **$P < .01$; absence of * or ** indicates nonsignificance.

(LRT [1 df] = 14.21, $P < .01$). Thus, regardless of whether the baseline psychosis diagnosis was primary or substance induced, common clinical features predicted remission at the 1-year time point. However, a diagnosis of drug dependence at baseline was not related to remission (LRT [1 df] = 3.52, nonsignificant).

Interaction of Baseline Clinical Variables and Diagnosis Type in Remission Outcome

Interactions of baseline clinical variables (duration of untreated psychosis, PAS scores, PANSS total score, SUMD awareness and misattribution scores, and diagnosis of substance dependence) with diagnosis type (primary psychosis or substance-induced psychosis) in predicting remission outcome were investigated. Results are shown in table 3. Every interaction test produced a nonsignificant result.

Key Baseline Predictors of Remission Outcome

We conducted a multivariate logistic regression to identify the key baseline predictors of remission outcome. The key predictors are the variables that made unique contributions to the prediction of remission after adjusting for the other variables. We present 2 versions of the multivariate logistic regression models in table 4 . The first, which we call Model 1, includes all 6 variables from table 2 that showed associations with remission. The second, which we call Model 2, is constructed by stepwise regression to include only variables that remain statistically significant after adjusting for the other variables in the model.

In Model 1, diagnosis type (OR = 2.63; 95% CI = 1.47, 4.71), duration of untreated psychosis (OR = 0.97; 95% CI = 0.95, 0.988), and total PANSS score (OR = 0.98; 95% CI = 0.97, 0.999) are significant after adjusting for all 6 clinical variables and diagnosis. Model 2 allows us to check if the colinearity among the nonsignificant variables might have resulted in a conservative adjustment. In this model, PAS score (OR = 0.13; 95% CI = 0.02,

Table 3. Assessment of Interactions of Baseline Predictors With Diagnosis Type on Remission at 1 Year

Interaction Term	LRT (1 df)	*P* Value
PANSS by diagnosis type	0.005	.94
Premorbid by diagnosis type	0.09	.76
Misattributions by diagnosis type	0.08	.77
Unawareness by diagnosis type	0.002	.96
Duration of psychosis by diagnosis type	0.266	.61
Drug dependence by diagnosis type	0.100	.75

Note: df, degrees of freedom.

Table 4. Multivariate Logistic Regression Analysis for the Relationship of Diagnosis Type and Baseline Clinical Variables to Remission at 1 Year

	Model 1		Model 2	
Variables	*B* (SE)	OR (95% CI)	*B* (SE)	OR (95% CI)
Diagnosis type[a]	0.97 (0.30)	2.63 (1.47, 4.71)	0.87 (0.28)	2.39 (1.39, 4.11)
Any drug dependence	−0.22 (0.30)	0.80 (0.44, 1.46)		
Duration of untreated psychosis	−0.03 (0.01)	0.97 (0.95, 0.988)	−0.03 (0.01)	0.97 (0.95, 0.997)
Total PANSS score	−0.02 (0.01)	0.98 (0.97, 0.999)	−0.02 (0.01)	0.98 (0.97, 0.987)
PAS score	−1.89 (0.97)	0.15 (0.02, 1.01)	−2.02 (0.97)	0.13 (0.02, 0.88)
Misattribution of symptoms score	−0.08 (0.09)	0.92 (0.77, 1.11)		
Unawareness of symptom scores	−0.13 (0.11)	0.88 (0.71, 1.08)	−0.18 (0.09)	0.84 (0.71, 0.993)

Note: Model 1—all effects are adjusted for other variables in the model: diagnosis type, any drug dependence, duration of untreated psychosis, total PANSS score, PAS score, misattribution of symptoms score, and unawareness of symptom scores; Model 2—stepwise selection: holding diagnosis constant, remaining significant variables are duration of untreated psychosis, total PANSS score, PAS score, and unawareness of symptoms score.
[a]Diagnosis type: 1, primary psychosis disorder; 2, substance-induced disorder.

0.88) and the SUMD unawareness of symptoms score (OR = 0.84; 95% CI = 0.71, 0.993) were also significant, and duration of untreated psychosis and total PANSS score remain significant.

Discussion

In this analysis, we examined predictors of 1-year remission of psychosis for participants with a baseline diagnosis of primary psychotic disorder or substance-induced psychosis. Baseline diagnosis was the strongest predictor of remission at 1 year: Half again as many participants with substance-induced psychosis were in remission compared with those with primary psychosis. Such a marked difference provides evidence that these 2 diagnostic groups differ not only on baseline characteristics[28] but also on outcome. Substance-induced psychosis appears to have a more benign course. However, patients with substance-induced psychosis at baseline who had specific risk factors experienced a different clinical course and were more likely to have met criteria for primary psychosis upon follow-up.[37] A longer duration of follow-up is needed to determine if differing patterns of psychosis remission in these 2 diagnostic groups persist over time.

For the first time, we showed that the same core group of baseline variables—better premorbid adjustment, shorter duration of untreated psychosis, better insight into psychosis, and lower severity of symptomatology on the PANSS total score—predicted remission at 1 year for both patients with substance-induced disorder and patients with primary psychotic disorder. There was no evidence of an interaction of a baseline predictor with diagnosis type in determining psychosis remission. This indicates that our findings apply both to patients with primary psychosis and to patients with substance-induced psychosis. However, even after adjusting for these clinical variables, the diagnostic distinction between primary psychosis and substance-induced psychosis remained significant, although it was reduced in magnitude. The OR for diagnosis after adjustment was 2.63, reduced from 3.29 before adjusting for clinical variables. This suggests that clinical characteristics associated with the difference between primary and substance-induced psychoses account for some of the difference in remission outcome.

These findings are consistent with many previous reports on schizophrenia: better preillness functioning, briefer and less profound psychosis, more intact ability to understand the illness, and greater stress leading to psychosis (substance use) have long been identified as indicators of a more favorable prognosis.[38] The unique finding in our data is that the same indicators predict remission of psychosis as an outcome of substance-induced psychosis.

The similarity of prediction factors for both diagnostic groups suggests similarity of underlying neurobiological vulnerabilities. That is, the same indicators may predict 1-year psychosis outcomes because they are markers for psychosis vulnerability. The stress-diathesis model[39] suggests that substance abuse may precipitate psychosis among some people who would otherwise be vulnerable but not psychotic. Caspi et al[40] have elegantly demonstrated this relationship by showing that individuals who are vulnerable to schizophrenia because of a specific polymorphism of the catechol-*O*-methyltransferase gene (val-val) increase their vulnerability if they are heavy cannabis users in adolescence. A second possibility is that psychosis may emerge earlier in vulnerable individuals who would otherwise develop the illnesses later. Yet another possibility is that individuals who are in the early phases of developing a psychotic disorder use substances

as a coping strategy of some type, which obscures the emerging diagnostic reality.

Further investigation of the genetic, environmental, and pathophysiological mechanisms underlying all types of psychotic disorders is warranted. It is likely that there are similarities in these mechanisms for both primary psychoses and substance-induced psychoses and that substance use is a common stress on the background of varying diathesis. The alternative view—less supported by the data—is that psychotic severity in substance-induced psychosis is related to the effects of specific substances or to the severity of substance-use disorder.[41–43]

Psychosis in response to drug use almost certainly represents a vulnerability marker. It may be one of the best markers that we currently have, especially if it is combined with the predictor variables highlighted in this study. The current emphasis on early treatment of schizophrenia[44,45] needs to be expanded to include early treatment of substance-induced psychoses. Unlike prepsychotic individuals, who are sometimes targeted for early interventions, those with substance-induced psychosis are experiencing symptoms, seeking treatment, and manifesting clear-cut signs of vulnerability—important clinical realities that attenuate the ethical concerns related to early intervention.

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