Reducing Dropout in Treatment for Depression:
Translating Dropout Predictors Into Individualized Treatment Recommendations

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ABSTRACT

Objective: Premature discontinuation of therapy is a widespread problem that hampers the delivery of mental health treatment. A high degree of variability has been found among rates of premature treatment discontinuation, suggesting that rates may differ depending on potential moderators. In the current study, our aim was to identify demographic and interpersonal variables that moderate the association between treatment assignment and dropout.

Methods: Data from a randomized controlled trial conducted from November 2001 through June 2007 (N = 156) comparing supportive-expressive therapy, antidepressant medication, and placebo for the treatment of depression (based on *DSM-IV* criteria) were used. Twenty prerandomization variables were chosen based on previous literature. These variables were subjected to exploratory bootstrapped variable selection and included in the logistic regression models if they passed variable selection.

Results: Three variables were found to moderate the association between treatment assignment and dropout: age, pretreatment therapeutic alliance expectations, and the presence of vindictive tendencies in interpersonal relationships. When patients were divided into those randomly assigned to their optimal treatment and those assigned to their least optimal treatment, dropout rates in the optimal treatment group (24.4%) were significantly lower than those in the least optimal treatment group (47.4%; $P = .03$).

Conclusions: Present findings suggest that a patient's age and pretreatment interpersonal characteristics predict the association between common depression treatments and dropout rate. If validated by further studies, these characteristics can assist in reducing dropout through targeted treatment assignment.

Trial Registration: Secondary analysis of data from ClinicalTrials.gov identifier: NCT00043550

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Most psychiatric patients respond to appropriate psychotherapeutic or psychopharmacologic treatment,[1] but 1 patient in 5 drops out before treatment completion.[2] Although many reasons for dropout exist,[3] those who leave treatment prematurely are likely to have poorer outcomes.[4–7] Given significant heterogeneity between studies, patient- or study-level moderators may account for differential dropout rates.

Thus, it is important to identify individuals at risk for dropout before beginning treatment. Age, gender, education, ethnicity, and socioeconomic status have been suggested to influence dropout rates,[8–11] with age being the only consistent predictor across different analyses.[2] Apart from demographic factors, type of treatment has also been considered to affect dropout, although meta-analyses have reported that dropout rates were not predicted by treatment.[2] However, meta-analyses allow inferences regarding only average samples and cannot determine whether different treatments are more or less tolerable to individual patients. To reduce dropout, it would be useful to determine whether one treatment is more acceptable than another to a particular subgroup of patients, thereby assigning treatment based on a "specific" rather than an "average" patient.

In the current study, we used systematic exploratory analyses to broaden our understanding of pretreatment patient characteristics that influence differential dropout rates among 3 treatments for depression. Demographic and interpersonal characteristics were selected based on research supporting an effect on dropout and were examined simultaneously rather than as a single moderator.[12] Factors included age,[13–16] gender,[14] education,[14–16] income,[13,17] ethnicity,[13,15,16] marital status,[14,18] preferred treatment,[19] severity of depression,[20] and personality disorders.[21,22] These variables were examined as predictors of dropout from pharmacologic and psychotherapeutic interventions for depression, using data from a randomized controlled trial (RCT) (ClinicalTrials.gov identifier: NCT00043550) conducted from November 2001 through 2007 that compared 3 treatments for depression: supportive-expressive therapy (SET), antidepressant medication + case management (MED), and placebo + case management (PBO). The trial failed to find significant differences among treatment conditions.[23] This is consistent with previous meta-analyses of treatments for depression[24–27] and with psychopharmacologic treatments attributing a rise in failed trials to increases in placebo effect.[28] These findings emphasize the importance of focusing on personalized treatment (which treatment is most effective for whom), rather than finding the best treatment for the "average" depressed patient.

Because interpersonal patient characteristics affect dropout and treatment outcome (as shown in this RCT and other datasets),[29,30]

Clinical Points

- Although 1 patient in 5 drops out before treatment completion, very little is known regarding patient characteristics that can be used by clinicians to provide the most appropriate treatment for their patients, thereby reducing dropout.
- The findings suggest that patient's age and pretreatment interpersonal characteristics can assist in reducing dropout through targeted treatment assignment.

we also examined whether interpersonal distress[31] and pretreatment alliance expectations emerge as moderators of dropout from treatment. Furthermore, we evaluated the potential clinical utility of the proposed approach for minimizing dropout through systematic treatment assignment.

Prior studies have focused either on predictors of dropout (prognostic variables) or on moderation effects, using inappropriate statistical methods.[13] This study is the first to systematically examine moderators of the association between treatment assignment and dropout using the interaction between treatment condition and potential prescriptive variables, allowing identified patient characteristics to be used clinically to facilitate personalized treatment selection.

METHODS

Participants

Patients diagnosed with primary major depressive disorder (MDD) determined by the Structured Clinical Interview for *DSM-IV* Axis I Disorders[32] were randomly assigned to 1 of 3 treatment conditions: SET, MED, or PBO (N = 156). Inclusion criterion was 17-item Hamilton Depression Rating Scale (HDRS) score < 14. Exclusion criteria included psychosis and high suicide risk.[23] Mean age was 37.5 years (standard deviation = 12.2 years); 59% of participants were female; 48% were white, 45% were African American, 5% were Latino, and 2% were Asian. At intake, 84.5% of patients had at least 1 comorbid Axis I disorder (44.9%, anxiety disorders; 35.3%, current substance abuse or past dependence disorder), and 46.2% had a comorbid Axis II personality disorder. The study was approved by the Institutional Review Board of the University of Pennsylvania, Philadelphia, and all patients provided written informed consent.

Treatments

Treatment was provided for a total of 16 weeks. Patients treated with SET (n = 51) received 20 sessions of manualized short-term psychodynamic therapy for depression.[33] In the MED (n = 55) and PBO (n = 50) conditions, patients received either sertraline (50–200 mg) or placebo, delivered by experienced psychopharmacologists following a manualized clinical management protocol.[34] Nonresponders were switched to venlafaxine (75–375 mg; MED) or to another placebo (PBO) after 8 weeks.

Measures

Prerandomization measures included the following:

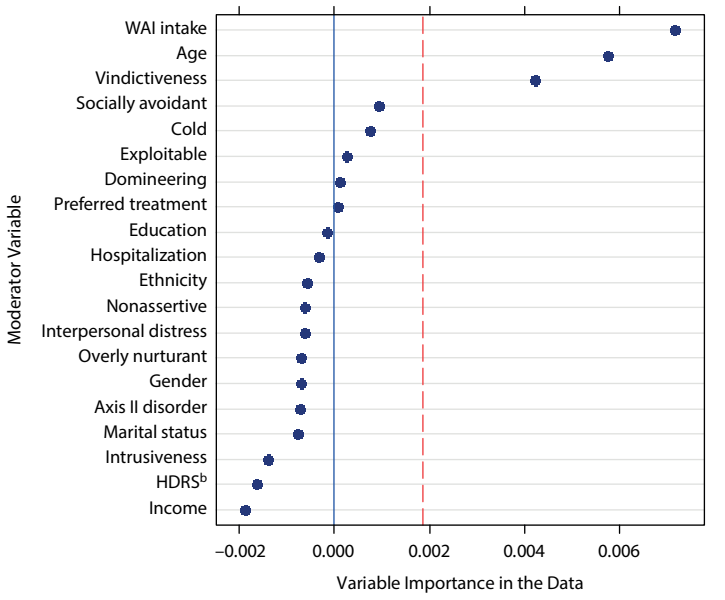
1. 17-item HDRS[35];
2. 64-item Inventory of Interpersonal Problems-Circumplex (IIP-C),[31] which measured interpersonal distress and patterns of relating. Total item mean represents a general level of interpersonal distress; octant means suggest a specific pattern of interpersonal problems. Cronbach α for each octant and total IIP-C score ranged from 0.73 to 0.95;
3. 12-item Working Alliance Inventory (WAI),[36,37] which assessed alliance expectations (Cronbach α = 0.93). Based on Barber et al, the instructions were changed as follows: "Because you have not yet experienced treatment through this study, answer the following questions, thinking about how you expect treatment to be"[38];
4. 113-item Structured Clinical Interview for *DSM-IV* Axis I Disorders, Patient Edition (SCID-I/P, Version 2.0),[32] which assessed personality disorders. Personality pathology was recorded as presence or absence of disorder;
5. a single forced-choice item,[39,40] which assessed patient preference for psychotherapy ("talking treatment") or medication ("drug treatment"); and
6. patient's age, gender, education level, salary, ethnicity, and marital status.

Dropout was defined as failure to complete the 16-week treatment protocol.

Statistical Analysis

First, we identified robust moderators of the association between treatment condition and dropout. We used the bootstrap-aggregation of model-based recursive partitioning by the random forest algorithm, as implemented in the R package "mobForest" (version 1.2).[41] In this method, a thousand model-based trees (ie, pathways for determining the variables that best predict dropout in different treatment conditions) were constructed based on bootstrapped samples from the primary dataset. For each tree, the model-based recursive partitioning searches for binary splits in the sample (eg, age ≥ 40 years vs < 40 years) that result in the model parameters on 1 side of the split being most different from model parameters on the other side of the split (eg, treatment A has relatively more dropout among age ≥ 40, but relatively less dropout among age < 40). Namely, splits are instances whereby treatment condition has a different relationship to dropout for a specific variable, indicating the presence of a statistically significant moderator of dropout by treatment condition. We used a random sample of partitioning variables for splitting at each node (ie, potential split-point). In each leaf (ie, split) of the tree, we estimated the dropout proportions for each treatment by a logistic regression with 2 dummy variables for comparing each active treatment (SET, MED) with the placebo. Final model predictions were obtained by aggregating across the

Figure 1. Variable-Importance Plot for the Bootstrapped Model–Based Recursive Partitioning Trees[a]



[a]The horizontal axis represents the average increase in classification accuracy gained by using the specific variable in the "real" data compared to use of the specific variable in permuted (ie, "mixed up" or fake) data. Positive values indicate that a variable not only predicts dropout outside of a given bootstrapped sample, but that it performs better than random noise. The dashed red line represents the random noise of all potential moderator variables and is constructed using the absolute value of the worst predictor. Variables to the right of the dashed red line are selected for later modeling.
[b]Pretreatment HDRS level.
Abbreviations: HDRS = Hamilton Depression Rating Scale, WAI = Working Alliance Inventory.

trees. The minimum α level for splits was set to .10, and the minimum leaf size for splitting was set to 15 patients.

To identify the robustness of potential moderator splits, we constructed a variable-importance plot using the conditional permutation scheme,[42] involving prediction within each tree for patients *left out* of building a given tree. To rank the moderators according to their importance in producing accurate predictions, we calculated an *importance statistic* that reflects the contribution each variable makes to classifying or predicting the target variable. The importance statistic is a way of estimating the out-of-sample predictive significance of all tested variables. The statistic reflects the improvement in prediction using the variable in cases "held out" of a given bootstrapped sample, compared to using permutations of "fake" data to make the same prediction. We tested robustness of the predictive value of a particular variable by examining the variables that had an importance statistic above the absolute value of the lowest ranking predictor. Moderators that were predictive only within subsamples of our data—but not to the validation samples—were excluded from further analysis. Although the bootstrapped scheme is exploratory, using it to select variables results in stable predictors that are less sensitive to the unique features of a given data set.

At the second step, we used the robust moderators identified in the first step in a logistic regression predicting the risk of dropout. We included the interactions of each predictor with 2 dummy variables of treatment condition, together with their main effects, in the logistic model. Following the methods of DeRubeis and colleagues,[12] we used leave-1-out cross-validation,[43] in which *n* logistic models were estimated, each with 1 patient left out (ie, a number of models equivalent to our sample size). Each model was used to estimate the risk of dropout for the patient who was left out of a given model, if the patient were to be assigned to each of the 3 treatments. This technique reduces bias and produces nominally more population-accurate coefficient weights because the patient with regard to whom the prediction is made is not included in the model estimation. The predicted risk of dropout for the treatment that the patient actually received is termed *factual prediction*. Estimates of the patient's risk of dropout in the 2 treatments that the patient did not receive are termed *counterfactual predictions*.[12] Thus, for each patient, we have 1 factual and 2 counterfactual predictions.

At the third step, we tested the within-sample utility of the model for reducing dropout through treatment assignment. We compared the difference in dropout frequency between patients who had been randomly assigned to the treatment with the lowest dropout probability according to the logistic model in which they were left out (ie, their clinical data did not contribute any information) versus those assigned to the treatment with the highest dropout probability.[12] On the basis of predicted scores from the second step, we estimated (1) the "true error" of the factual predictions (ie, the mean of the absolute value of the difference between the observed score of whether the patient dropped out and factual predictions of the risk for dropout), (2) the standard error of the set of predictions, and (3) the personalized advantage index.[12] The personalized advantage index represents the magnitude of the predicted difference (ie, predicted advantage) for each patient randomly receiving the treatment with the lowest predicted risk for dropout (optimal) versus receiving the treatment with the highest predicted risk for dropout (least optimal).[12]

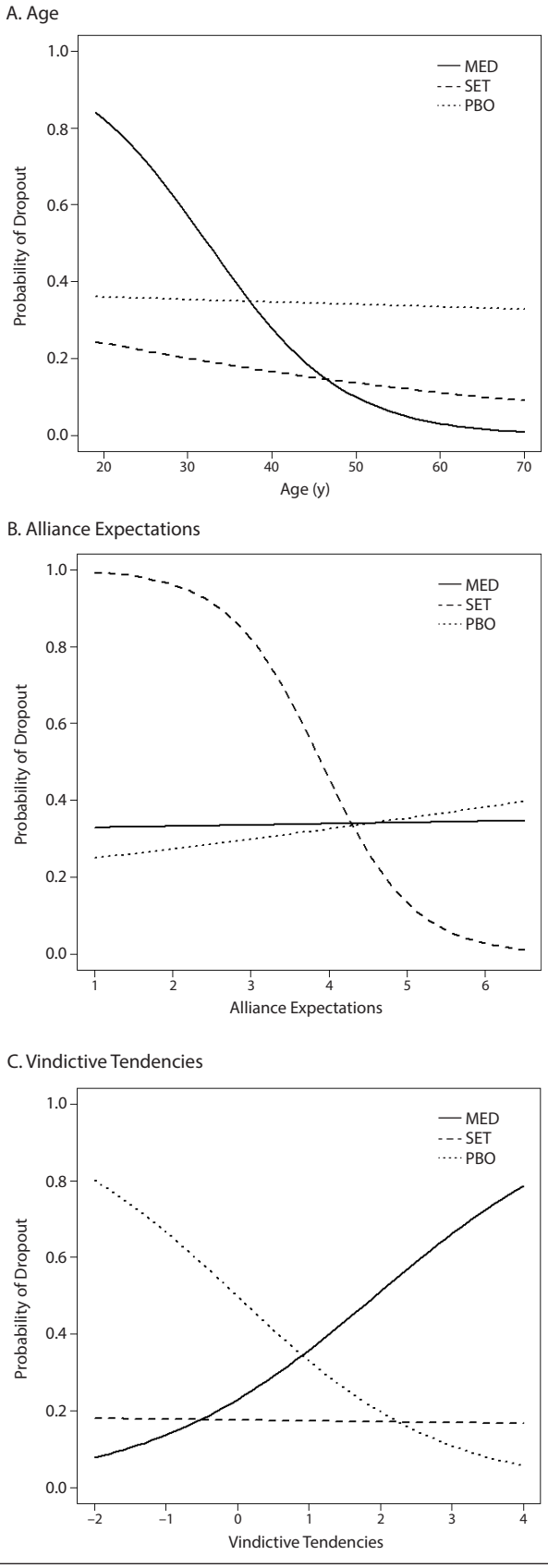
Analyses were conducted twice: once on patients who had no missing observations (n = 126) and once on the full dataset, after multiple imputation of missing observations (N = 156). Using the Markov chain Monte Carlo method,[44] we repeated our analyses on 20 imputed datasets.[45] We repeated all 3 steps for each imputed dataset and averaged the results. In the present data, we did not reject the hypothesis that the observations were missing completely at random (Little MCAR test: $\chi^2_{104} = 122.510$, $P = .11$) and, therefore, anticipated similar findings.

RESULTS

General Differences Between Treatment Conditions in Dropout

Fifty-four patients (34.6%) dropped out before 16 weeks, irrespective of treatment condition (MED: 40.0% [n = 22],

Figure 2. Expected Dropout Probability as a Function of Age, Alliance Expectations, and Vindictive Tendencies



Abbreviations: MED = antidepressant medication + case management, PBO = placebo + case management, SET = supportive-expressive therapy.

SET: 23.5% [n = 12], and PBO: 40.0% [n = 20]; $\chi^2 = 4.11$, $P < .13$, N = 156). Pairwise differences in dropout rates between treatments were not statistically significant, with an odds ratio of 2.17 (95% CI, 0.93–5.03; $\chi^2_1 = 3.24$, $P = .07$) for MED versus SET and 2.17 (95% CI, 0.92–5.12; $\chi^2_1 = 3.11$, $P = .07$) for PBO versus SET. Time to dropout was similar among treatments ($\chi^2_6 = 10.1$, $P < .12$, N = 156), whether before treatment (MED: 7.3% [n = 4], SET: 9.8% [n = 5], and PBO: 4.0% [n = 2]), at or before midtreatment assessment (MED: 29.1% [n = 16], SET: 11.8% [n = 6], and PBO: 26.0% [n = 13]), or between midtreatment and 16 weeks (MED: 3.6% [n = 2], SET: 2.0% [n = 1], and PBO: 10.0% [n = 5]).[23]

Predictors of Differential Dropout for Treatment Conditions

We conducted analyses first on a subset of the data with all observations (n = 126). The random forest analysis identified age, alliance expectations, and vindictiveness (IIP-C octant) as robust moderators of dropout between treatments. Figure 1 shows the resulting variable-importance plot.

Next, the 3 identified variables and their interactions with the 2 dummy variables of treatment condition (SET vs PBO, MED vs PBO) were entered into a single logistic regression to predict dropout. Three significant interactions were found (Figure 2): (1) between age and MED (β = −0.12, standard error [SE] = 0.05, $P = .02$), with greater risk of dropout for younger patients in MED than in PBO; (2) between alliance expectations and SET (β = −1.81, SE = 0.90, $P = .04$), with lower risk of dropout for patients with higher expectations of a strong alliance in SET than in PBO; and (3) between vindictive interpersonal tendencies and MED (β = 1.32, SE = 0.56, $P = .02$), with greater risk of dropout for patients with more vindictive tendencies in MED than in PBO. To compare SET with MED, we conducted another logistic regression for predicting dropout, using 2 other dummy variables of treatment condition: SET versus MED and PBO versus MED. These analyses revealed an additional significant interaction between alliance expectations and SET (β = −1.70, SE = 0.86, $P = .04$), with lower risk of dropout for patients with higher expectations of a strong alliance in SET than in MED.

Third, we predicted a given patient's likelihood of dropout in each treatment condition using all 3 moderating variables. We used a leave-1-out logistic model to estimate the risk of dropout for each patient, based on estimates from a "left-out" model to which their clinical data did not contribute any information. We compared the difference in dropout frequency between patients randomly assigned to their estimated optimal treatment (24.4%) and those assigned to their less optimal (28.6%) and least optimal treatment (47.4%). The dropout rate for patients assigned to their least optimal group was significantly higher than for patients assigned to their less optimal or optimal treatment ($P = .03$ for optimal vs least optimal; Table 1). The predicted advantage (the difference between the estimated probability of dropout in the least optimal and optimal groups) for the full sample was 0.45 ± 0.19.

Table 1. Regression Coefficients for the Logistic Regression Predicting Dropout on the Complete Dataset

	Coefficient	SE	*Z* Value	*P*
Intercept	0.3469	−3.253	−1.1285	.00114
Less optimal	0.2122	0.4868	0.436	.66295
Least optimal	1.0231	0.4753	2.153	.03134

Abbreviation: SE = standard error.

To account for the possible influence of missing data, we repeated the above analyses on multiple imputed datasets. Similar results were obtained. Specifically, the same 3 robust predictors of dropout emerged, model coefficients and predicted probabilities averaged across all imputed datasets were highly similar, and very similar percentages of dropout were obtained for patients assigned to their optimal (29.4%), less optimal (28.1%), and least optimal treatment (50.0%), the least optimal group dropping out of treatment significantly more often than the other 2 groups ($P = .03$).*

DISCUSSION

The present study explored how patients' pretreatment characteristics may guide their optimal assignment to treatment to reduce dropout rates. Findings suggest that patients randomly assigned to their model-determined optimal treatment were significantly less likely to drop out than were those assigned to their least optimal treatment.

Consistent with our general hypothesis that a patient may be more likely to continue in one particular treatment for depression than in another, patients' pretreatment characteristics interacted with treatment condition to predict dropout. Among assessed factors, age, alliance expectations, and vindictiveness (hostile dominance, distrust of others, and suspiciousness toward others) were found to be significant moderators of dropout.

Two novel findings of this study are that patients with higher expectations of a strong alliance[38] had a lower risk for dropout in SET than in either MED or PBO conditions. Furthermore, patients with higher levels of vindictiveness had a greater risk for dropout in MED than in PBO. These findings underscore the importance of pretreatment interpersonal factors in predicting dropout and are consistent with existing research recognizing how interpersonal relationship patterns can explain a patient's ability to form a satisfactory alliance.[46,47] Our findings are also consistent with those of Sharf et al,[48] in which a weaker alliance throughout treatment was associated with increased dropout.

Previous studies have examined the demographic variables that we explored (eg, gender, education, ethnicity), but only as predictors of dropout within a single treatment or across multiple treatments, rather than as factors leading patients to tolerate one treatment over another. Moderator analyses are more useful than single prognostic predictors of dropout because they offer ways to improve treatment retention for specific patient subgroups. By contrast, identifying general risk factors for dropout does not provide a clinical recourse to *prevent* dropout. Optimizing the patient's ability to remain in treatment is of paramount importance. If these findings are replicated, they can assist in clinical decision-making.

Rather than considering placebo effect as a nuisance, we examined potential moderators of the placebo effect for both research and clinical use.[49] The primary analyses for this trial found different symptomatic outcomes across treatments, including placebo, based on minority status and gender.[23] Over the past 30 years, the placebo effect has increased about 7% per decade[50] and is one of the primary reasons for the increase in "failed" antidepressant trials.[51,52] It is imperative that we develop methods for minimizing placebo response in RCTs and maximizing it in clinical practice.[28] Understanding the psychological and neurobiological circumstances that promote a positive response to an inert medication (placebo) will allow us to adjust treatments accordingly.

The study has several limitations, the most important being its exploratory nature. Without a priori hypotheses, a total of 20 predictors were examined in a moderate sample size of 156 patients. Although the clinical relevance of these findings requires validation in future research, we employed methods increasing the likelihood that these relations will replicate. Specifically, the included variables were selected by random forest bootstrapping based on their internal consistency across the sample. Predictions were made with leave-1-out cross-validation, thus enhancing the chance of these relationships being replicated out-of-sample. Furthermore, although the dominant reason for dropout in manualized treatment is treatment failure or intolerance, other reasons certainly exist (eg, family and geographic reasons).[3]

To fully understand the clinical applications of any treatment selection approach, the approach should be applied prospectively.[12] Future research should examine the importance of the moderators identified in this study, as well as other potential moderators[53,54] for various treatments and patient populations.

Overall, the present study is the first to systematically examine moderators of the association between treatment assignment and dropout (prescriptive variables). It represents an important step in the effort to reduce treatment dropout through targeted treatment assignment, using evidence-based decision-making,[55] and adds to the growing empirical research on personalized treatment.[56]

*Given that treatment conditions interacted with gender and minority status to produce different outcomes in this RCT,[23] we also examined whether allowing the model to select an interaction of gender and minority affects the findings. Findings suggest that the inclusion of this interaction did not have any effect on the findings because the interaction was not chosen as a robust moderator of dropout.

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Drug names: sertraline (Zoloft and others).

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