Prediction of Response to Antipsychotic Drugs in Schizophrenia Patients within the Early Phase of Treatment

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ABSTRACT:

Prediction of response to antipsychotic drugs in schizophrenia patients within the early phase of treatment

Objective: Currently, schizophrenia guidelines recommend waiting for 3 to 6 weeks before considering a patient as non-responder. However, recent studies indicate that the response to antipsychotic medications starts within the first two weeks of treatment. The aim of this study is to determine the predictive value of early improvement at 2 or 4 weeks for non-response at 6 weeks.

Methods: Twenty seven in- and out-patients with a diagnosis of schizophrenia according to DSM-IV, between the ages of 18 to 65 years, who were moderately-to-severely ill (baseline Positive and Negative Syndrome Scale (PANSS) total score ≥ 75, with at least "moderate" level of severity / score>4 on at least 2 of the 4 Brief Psychiatric Rating Scale (BPRS) psychotic cluster items) were included. Ten patients were receiving antipsychotic treatment for the first time, and 17 patients' treatment was changed due to non-response to prior antipsychotic treatment. The patients were evaluated with the PANSS and the Clinical Global Impression-Severity (CGI-S) scale at 0, 2, 4 and 6 weeks of antipsychotic treatment. Non-response at endpoint was defined in 3 different ways to reflect the variations in the level of response to medication: "not minimally improved", "not much improved" and "not remitted". As previously described, "not minimally improved" and "not much improved" were defined as less than 28% and 53% improvement in the PANSS total scores, respectively. "Not remitted" was defined according to the criteria developed by "The Remission in Schizophrenia Working Group" without the time criterion. Signal detection methods using receiver operating characteristics (ROC) curves were implemented to detect the optimal threshold of early non-response at 2 and 4 weeks. Total accuracy, sensitivity, specificity and positive and negative predictive value of cut-off points were calculated for predicting "not minimally improved", "not much improved" and "not remitted" at endpoint.

Results: The early response threshold for predicting "not minimally improved' was less than 15.3% reduction in PANSS total score at week 2, less than 15.5% reduction at week 4. The early response threshold for predicting "not much improved" was less than 22.1% reduction at week 2 and less than 44.3% reduction at week 4; for "not remitted" was less than 17.5% reduction at week 2 and less than 23.2% reduction at week 4. Specific thresholds of "much improvement" and "remission" were not identified at week 2, whereas thresholds calculated for week 4 had good discriminative power.

Conclusion: The findings of this study did not support the findings of earlier studies indicating that non-response at 2 weeks accurately predicts subsequent lack of response in patients with schizophrenia. Instead, the findings revealed that non-response could best be predicted at 4 weeks as in some other previous studies. The question of which time point for early prediction of response could be best predicted in schizophrenia patients needs to be further addressed in subsequent studies with larger sample size.

Keywords: schizophrenia, early response, antipsychotics, prediction

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INTRODUCTION

Schizophrenia is a common and debilitating illness, characterized by chronic psychotic symptoms and psychosocial impairment[1]. The treatment of schizophrenia is an ongoing challenge in psychiatry. In the treatment of schizophrenia, how long an initial antipsychotic trial should last or when to change the initial antipsychotic regimen is a critical question and remains unanswered[2]. For years, the onset of action of antipsychotics has been accepted as "delayed", but recent studies have shown that antipsychotic efficacy starts early in the treatment and most of the improvement is seen within the first weeks of treatment[3,4]. Subsequent studies demonstrated that this was true for both first episode and chronic schizophrenia patients[5].

Thus, in patients with schizophrenia, early response to antipsychotics was shown to be a predictor of clinical response and subsequent global functioning in some studies[6,7]. More importantly, later studies have identified that early non-response to antipsychotics is a predictor of ultimate non-response[8,9]. In view of the fact that, early non-response predicts later non-response, this might have clinical implications. If a clinician knows that the treatment will be ineffective early in the treatment, a decision about changing the antipsychotic can be made earlier. This critical decision will avoid unnecesssary treatments and associated side effects, optimize the patients' treatment regimen and reduce illness burden and costs[10].

To date, several studies have been conducted in order to accurately predict both response and non-response to antipsychotics early in the treatment. However, there is no clear consensus about how to define early response, subsequent response and remission. Treatment response was defined as 20-50% improvement in clinical rating scales by different researchers[7,8]. Previously, it was not clear what given scores in Positive and Negative Syndrome Scale (PANSS) mean from a clinical point. Leucht and colleagues correlated Clinical Global Impression (CGI) scores to PANSS[11]. With regard to CGI, "mildly ill" approximately corresponded to a PANSS total score of 58, "moderately ill" to a PANSS of 75, "markedly ill" to a PANSS of 95 and severely ill to a PANSS of 116. To be "minimally improved" according to the CGI score was associated with a mean percentage PANSS reduction of 19%, 23%, 26% and 28% at weeks 1, 2, 4 and 6, respectively. In a similar vein, to be "much improved" according to CGI score was associated with a mean percentage PANSS reduction of 40%, 45%, 51% and 53% respectively.

Different definitions were also being used to define "remission" in schizophrenia. In 2005, "The Remission In Schizophrenia Working Group" proposed operational criteria to define remission[12]. These operational criteria define remission according to disease severity and duration of remission.

In studies focusing on early prediction of antipsychotic response, duration of follow-up varies between 4 weeks to 6 months. Besides, early response was usually measured in the first or second week, though it varies between studies[2,7,13-23].

In a metaanalysis distinguishing schizophrenic patients according to illness severity, signal detection method was used to obtain optimal thresholds of early response to antipsychotics[15]. Early response in weeks 1-to-4 was used to predict later response at week 8. In moderately-to-severely ill patients, the early response threshold for predicting not 'minimally improved' was <15% reduction in PANSS total at Week 2, not 'much improved' was <23% at Week 2, and not 'remitted' was <26% at Week 4. For less than moderately ill patients, the optimal early response threshold for predicting not 'minimally improved' was <12% reduction in PANSS total at Week 2, and not 'much improved' was <14% at Week 1.

Most of the studies on early prediction of antipsychotic response demonstrated that later response/non-response can be predicted as early as two weeks in both chronic and first- episode patients with schizophrenia[13-18]. On the contrary, in a study evaluating response status in first-episode patients; it was shown that symptom severity show a progressive reduction in subsequent weeks and

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week 4 (but not week 2) was found to be associated with responder status at week 16 19.

Studies on early prediction of antipsychotic response have used different methodologies, patient populations and diverse definitions about treatment response and remission. Follow-up periods were also diverse. Therefore, inconsistency between results was inevitable. It is obvious that, new studies including schizophrenia patients with various degrees of severity in psychopathology are required to explore this special issue.

The aim of this present study was to determine the predictive validity of early improvement defined in PANSS totalscores at 2 or 4 weeks for non-response at 6 weeks.

METHODS

Participants

This prospective study was conducted at Hacettepe University, Faculty of Medicine, Department of Psychiatry between September 2009-January 2010. Patients with schizophrenia aged 18-65 years who demonstrated an acute exacerbation of psychotic symptoms and who accepted to participate the study were enrolled. Participants were not included in the study if they had a medical condition affecting the central nervous system, alcohol or substance abuse in the last 6 months, mental retardation and traumatic brain injury causing a loss of consciousness for more than 5 minutes. Forty-two schizophrenic patients were evaluated and eventually 27 patients with schizophrenia (in- and out-patients) diagnosed according to the DSM-IV criteria were included in the study[23]. As we intended to predict the antipsychotic response, we included patients who were moderately-to-severely ill. Moderately-to-severely ill patients were defined as folllows: baseline PANSS total score ≥75, with at least "moderate" level of severity (score ≥4) on at least 2 of the 4 Brief Psychiatric Rating Scale (BPRS) psychotic cluster items (i.e. conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content)[24]. The

study was appproved by Hacettepe University Faculty of Medicine Research Ethics Committee and written informed consent were obtained from all the participants prior to commencement of the study. The study was conducted in accordance with the Declaration of Helsinki.

The patients were evaluated with the PANSS and the Clinical Global Impression-Severity (CGI-S) scale at 0, 2, 4 and 6 weeks[25,26]. Non-response at endpoint was defined in 3 different ways to reflect the variations in the level of response to medication: "not minimally improved", "not much improved" and "not remitted". As previously described, "not minimally improved" and "not much improved" were defined as less than 28% and 53% improvement in the PANSS total score, respectively. "Not remitted" was defined according to the criteria developed by "The Remission in Schizophrenia Working Group" without the time criterion[12].

Measures

The Positive and Negative Syndrome Scale (PANSS): It is one of the most widely used methods for standardized measurement of schizophrenic core symptoms[25]. The PANSS consists of 7 positive symptom items, 7 negative symptom items, and 16 general psychopathology items. All individual items are scored on a 7-point Likert scale ranging from 1 to 7. The reliability and validity of the Turkish-language version of the scale were established by Kostakoglu et al.[27].

The Clinical Global Impression (CGI) scale: It has been widely used to measure clinical outcomes in symptom severity and treatment efficacy in subjects with psychoses[26]. The scale consists of three dimensions, illness severity, improvement and side-effects. This scale has ratings from 1 (not ill) to 7 (extremely ill).

Statistical Analysis

The SPSS 15.0 Software for Windows and Number Cruncher Statistical System (NCSS) were used for

the statistical analyses. Missing values was handled using the method of last-observation-carried-forward (LOCF) analysis. Signal detection methods using receiving operating characteristics (ROC) curves were implemented to detect the optimal threshold of early non-response at 2 and 4 weeks. Total accuracy, sensitivity, specificity, positive and negative predictive value of cut-off points were calculated for predicting "not minimally improved", "not much improved" and "not remitted" at endpoint. The Area Under the ROC Curve (AUC) ranges from 0.5 to 1 and AUC ≥0.8 indicates excellent discrimination, Since we intended to predict non-response with excellent discriminability, we used those thresholds obtained when AUCs were 0.8 or above[28].

RESULTS

Patient Charateristics

The mean age of the 27 patients was 32.2 (±11.5). Of the patients, 16 (59.3%) were male and 11 (40.7%) were female, 21 were (77.8%) outpatients and 6 (22.2%) were inpatients. Only seven of all patients (25.9%) was currently working at the time.

Table 1: Patients' baseline characteristics		
Age (Mean±SD)		32.2±11.5
Age at onset of illness (Mean±SD)		25.5±8.7
Education status (year) (Mean±SD)		11.0±2.8
Gender n (%)	Female	11 (%40.7)
	Male	16 (%59.3)
Employment status n (%)	Employed	7 (%25.9)
	Unemployed	20 (%74.1)
Marital status n (%)	Single	15 (%55.6)
	Married	10 (%37.0)
	Divorced	2 (%7.4)

Importantly, 10 patients (37%) were in the first episode of schizophrenia who were antipsychotic naive and 17 (63%) were chronic schizophrenic patients whose antipsychotic treatment changed due to exacarbation of psychotic symptoms. All patients were treated with atypical antipsychotics. Patients' baseline characteristics are presented in Table 1.

Treatment outcomes at week 6

Changes in PANSS and CGI-S scores by weeks are presented in Table 2. By week 6, 22(81.5%) of 27 patients were 'minimally improved' (28% cut-off); 10 (37%) were 'much improved' (53% cut-off), and 20 (74.1%) of patients were 'remitted'.

Optimal thresholds for predicting treatment outcomes

In general, AUC increased over time in the patients. For predicting not 'minimally improved', the AUC reached 0.8 at Week 2. For predicting not 'much improved' and not 'remitted', the AUC reached 0.8 at week 4. By using AUC to obtain excellent discriminative ability, the optimal early response threshold for predicting not 'minimally improved' at week 6 was <15.3% reduction in PANSS total score at Week 2. For predicting not 'much improved' at week 6, the optimal early threshold was <44.3% reduction in PANSS total score at week 4. Lastly, the optimal early response threshold for predicting not 'remitted' at week 6 was <23.2% reduction in PANSS total score at Week 2.

The optimal early thresholds for predicting

Table 2: Changes in Clinical Rating Scales and Treatment Response Rates				
	Week 0	Week 2	Week 4	Week 6
PANSS Total	101.56±16.66	85.67±18.30	69.30±20.22	56.70±22.40
PANSS Positive	27.85±4.87	21.96±6.00	17.26±6.35	13.22±6.95
PANSS Negative	25.07±6.88	22.19±6.61	18.07±6.06	15.30±13.00
PANSS General Psychopathology	48.63±7.73	41.59±8.58	33.67±10.29	28.19±11.40
CGI-S	5.22±0.75	4.07±0.99	3.37±1.27	2.63±1.57
Minimally improved	0	2 (%7.4)	19 (%70.4)	22 (%81.5)
Much improved	0	0	1 (%3.7)	10 (%37.0)
Remitted	0	2 (%7.4)	11 (%40.7)	20 (%74.1)

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Table 3: Optimal thresholds for predicting non-responseat week 6

Outcome measure	Treatment week	Early non-response threshold	AUC	Two-tailed probability value(p)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Total Accuracy (%)
Not "minimally improved"	2	<15.3	0.83	0.021	100	72.7	45.5	100	77.8
	4	<15.5	0.98	0.001	100	95.5	83.3	100	96.3
Not "much improved"	2	<22.1	0.62	0.292	82.4	50	73.7	62.5	70.4
	4	<44.3	0.82	0.006	100	60	80.9	100	85.2
Not "remitted"	2	<17.5	0.77	0.031	100	65	50	100	74.1
	4	<23.2	0.96	<0.001	85.7	95	85.7	95	96.3

AUC: Area under the Curve, PPV: Positive predictive value, NPV: Negative predictive value, Gray shading indicates the earliest time point when AUC≥0.8.

non-response at week 6 for 3 different outcomes are presented with sensitivity, specificity, positive predictive value, negative predictive value and total accuracy rates in Table 3.

DISCUSSION

This study evaluated inpatient and outpatient schizophrenia patients who were moderately-to-severely ill. The study group consisted of both first episode patients and chronic schizophrenia patients. The objectives of this study were to determine the predictive validity of early improvement in PANSS total scores at 2 or 4 weeks for non-response at 6 weeks and identify optimal thresholds for early improvement thatwould best predict subsequent response/nonresponse at week 6. It was demonstrated that the early response threshold for predicting "not minimally improved' was less than 15.3% reduction in PANSS total scores at week 2. The early response threshold for predicting "not much improved" was less than 44.3% reduction and for "not remitted" was less than 23.2% reduction at week 4. Specific thresholds of "much improvement" and "remission" were not identified at week 2, whereas thresholds calculated for week 4 had good discriminative power. The findings of this study did not support the findings of earlier studies indicating that non-response at 2 weeks accurately predicts subsequent lack of response in patients with schizophrenia. Instead, the findings revealed that non-response could best be predicted at 4 weeks as reported in some other previous studies.

Chen and colleguaes used moderately-to-severely ill patients similar to the present study to obtain optimal thresholds for early response15. It was indicated that <15% reduction in PANSS scores at week 2 predicted not "minimally improved" at week 8 with 73% sensitivity, 77% specificity, and 75% total accuracy rates. This value is close to the estimated value of 15.3% in the present study. There is no other study utilizing "minimally improved" as treatment outcome in the psychiatry literature. However; in some studies using close treatment response measures (25-30%), it was shown that early response (15.3-20%) could be used the predict the treatment response[8,9]. As a result, as shown in numerous studies, our study demonstrated that minimal improvement can be predicted from the second week of treatment with excellent discriminative power.

In the study by Chen and coleguaes, not "much improved" at week 8 was predicted by <23% improvement at week 2 with 74% sensitivity, 80% specificity and 75% total accuracy rates and by <45% improvement at week 4 with 93% sensitivity, 74% specificity and 90% total accuracy rates15. The threshold found in the present study for predicting not "much improved" at week 4 (44.3%) is close to threshold (45%) in the aforementioned trial. But, the threshold found by Chen and colleagues predicted not "much improved" with higher senstivity and total accuracy rates. This difference may arise from different sample size and patient selection criteria.

Kinon and colleguaes used a treatment

outcome measure as 50% reduction in PANSS scores similar to our "much improved" criterion[8]. They found that, early response (defined as 20% reduction in PANSS) at week 2 predicted the determined outcome with 68% sensitivity, 75% specificity, 33% PPV and 93% NPV. In another study, 31.9% reduction in BPRS scores at week 2 predicted non-response at week 4-6 with about %81 sensitivity, 74% specificity, 89% PPV and 59% NPV9. As the above stated two studies established cut-off points for predicting "much improved" at week 2, it was not possible to compare these findings with the present study. In a shorter period study, authors investigated whether early response (at week 2) predicted response at week 4 for olanzapine and risperidone[17]. Early response was defined as a CGI-Improvement score ≤3 and final response was defined as ≥50% reduction in PANSS scores. They determined that non-response to risperidone at week 2 predicted non-response at week 4 with about 97% sensitivity, 53% specificity, 81% PPV and 91% NPV. But olanzapine did not demonstrate a significant response until 4 weeks.

In addition, two studies have investigated whether early response to predict later response/ non-response was true for the patients with first episode psychosis. The first one demonstrated that early response (defined as ≥26.2% improvement in PANSS) strongly predicted later non-response (at week 12) with 63% sensitivity, 80% specificity, 77% PPV, and 66% NPV[17]. The latter, using a more stringent response criteria (e.g.,: absence of substantial positive symptoms) symptomatic change at week 4 (but not 2 or 8) was found to be associated with responder status at week 16 18. The sensitivity, specificity, PPV and NPV values fort he threshold in this study was about 62%, 51%, 60% and 58% respectively.

According to studies with chronic patients, NPV value was greater than PPV[2,8,13,14,16,17]. In consideration of NPV values, the literature suggests that 58% to 91% of early-non-responders will continue to be non-responders. For chronically ill patients NPV values were between 75% and 85%. In first-episode patients NPV values were were between 58% -66%[18,19]. Starting from this point, early non-response in a first-episode patient is not a strong predictor of final non-response. This gives support to the idea that first episode patients may experience a delayed response to antipsychotics[29]. While most studies compared here included patients with chronic schizophrenia, the present study included both chronic and first-episode patients. So, this difference might have a distinct effect when interpreting our results. As a consequence,while not all, but quite a few studies demonstrated that "much improvement" can be predicted from the second week of the treatment, we could barely predict it from the fourth week of treatment with excellent discriminative power.

If we look from the viewpoint of remission, research shows inconsistent results. In Chen and colleguaes' moderately-to-severely ill patients, 26% reduction in PANSS scores at week 4 (not at week 2) predicted remission at week 6 with 72% sensitivity, 77% specificity and 75% total accuracy[15]. Another study demostrated that 20% reduction in PANSS scores predicted remission with 53% sensitivity, 76% specificity, 72% PPV, 58 % NPV and 65% total accuracy14. Similarly, Kinon and colleagues showed that remission was predicted by early response (>20% reduction in PANSS) with 50% sensitivity, 80% specificity, 59% PPV, 73% NPV and 69% total accuracy[16]. The above mentioned study has an acceptable but lower AUC compared to our study (0.72 vs 0.96). Using the same remission criteria, 28.1% reduction in BPRS scores predicted non-remission at week 4-6 with about 70% sensitivity, 66% specificity, 41% PPV, and 70% NPV9. A naturalistic study looked for symptomatic remission at week 12 in patients with first-episode psychosis all treated with quetiapine. Patients were followed-up at weeks 2, 4, 8 and 1231. It was concluded that non-remission at week 8 was a strong predictor for not reaching remission at the end of the study. To sum up, while most of the studies demostrated that remission can be predicted fom the second week of the antipsychotic treatment, some of them did not support this. Additionally, it must be kept in mind that a few of them did not have excellent

discriminative power. In the present study, remission could be predicted at week 4, but not at week 2. This might possibly be due to small sample size of the present study. Secondly, our combined patient group with first-episode and chronic schizophrenia might have affected our results as it is mentioned that first-episode patients might have a delayed response. When assessing remission, we did not consider the time criterion proposed by the "Remission in Schizophrenia Working Group". There is a tendency to use the symptomatic remission criteria in related studies[8,15].

With respect to 3 different outcomes used in the present study; by week 6, 22 (81.5%) of 27 patients were 'minimally improved'; 10 (37%) were 'much improved', and 20 (74.1%) of patients were 'remitted'. Although showing significant improvement from baseline in severely ill patients, some of them did not remit. Thus, thresholds for "much improved" was higher than "remitted" at all time points. In Chen and colleguaes study, at the end of the 8th week, patients in the 'minimally improved', 'much improved', and 'remitted' groups were 39.8%, 9.2% and 30.2% respectively[15]. Differences in treatment outcomes could be due to small sample size of our study and heterogeneity of the patient population in the compared group and differences in treatment periods. Another study including 247 patients, used treatment outcomes as 40% reduction in PANSS scores and remission[14]. Initial PANSS scores were 75.8±18.8 and this study showed a 27% remission rate at week 2 and 54% remission rate at discharge. According to our study, remission rate was higher at week 2, but lower at discharge. Differences in initial PANSS scores and treatment periods might contribute to explain the variation of the results.

Together with the above discussed factors, two other factors might have a role in these different outcomes. Firstly, the studies compared here have certain differences regarding gender and ethnicity. As it is known that both gender[31] and ethnicity[32] might influence response to antipsychotics, both may have been additional factors contributing to the differences in response and remission rates observed in our study and other studies.

If we can predict treatment response earlier, this can guide clinicians in deciding how long the initial antipsychotic trial should last. Using this method, an alternative treatment option can come forth earlier during the course of treatment. While some studies reported that early antipsychotic change is associated with more frequent use of acute-care services including hospitalization and poorer economical outcomes[33]; one prospective study demonstrated that switching strategy in early non-responder group may lead to greater clinical improvement in some patients than staying on the same antipsychotic[2].

Hatta and colleagues investigated whether switching early responders to risperidone or olanzapine (at week 2) from the other would show greater improvement at week 4[17]. Early non-response to risperidone predicted non-response at week 4 but there was a significant response to olanzapine that did not occur until 4 weeks. Thus, in case of non-response in the early phase of treatment, it may be feasible to switch to another drug from risperidone earlier, but wait longer when olanzapine is the first drug. The same differential pattern could also be present for other antipsychotics agents and further studies with different antipsychotics should be conducted to assess this issue. As can be seen through the review of the mentioned studies, views regarding the best time period for predicting response to antipsychotics and the best switching strategies have not yet reached a conclusion.

Results from new and larger studies in this field may shorten the duration of the first antpsychotic trial in the current treatment guidelines or show that current treatment periods are optimal.

Limitations

The small sample size is the most important limitation of the present study. Another limitation of the study is the moderately-to-severely ill patient population. Since mildly ill patients are not included in this study, generalization of these

results is problematic. In addition, due to the design of this study, patients were evaluated in two week intervals, and therefore it is not possible to say whether non-response at 6 weeks can be predicted before week 4, for example at week 3.

Another limitation of the study is that it is confined to 6 weeks. In addition to studies determining treatment outcome at 6 weeks, some studies identify treatment outcome in longer periods. The longer period studies are rather re-analysis of comparative studies. As the basic aim of the early prediction studies are to specify non-response as soon as possible to decide for switching or not, 6 week period for this study may be considered acceptable.

The actual remission is defined as maintenance of remission at least 6 months. Related to remission, we only used the symptomatic remission part of the proposed criteria. The change in the time criterion is the common limitation of such studies.

Differences in design between studies, different inclusion/exclusion criteria, patient selection, tools used for assessment, different time points for early response and final response would also limit the comparison of the results.

CONCLUSION

In the present study, non-response to antipsychotic treatment in schizophrenia patients

at week 2 predicted "minimal improvement", but not "much improvement" and "remitted" at week 6. Non-response at week 4 predicted all of the three outcome measures. These results demonstrated that patients that will much improve or remit can not be predicted at week 2, but at week 4. These results are inconsistent with the studies predicting non-response and remission at the second week. Thus, our findings suggest to wait for at least 4 weeks to make a decision about the treatment outcome and switching. Studies in this field have differed in patient characteristics, time chosen for evaluations, study type, different time points for final evaluation, tools used for assessment and thresholds for early response and final response. Early prediction of response to antipsychotics remain an important question. The crucial questions at what time treatment response/non-response can be best predicted and whether or not patients without early improvement will benefit from a change of antipsychotic medication, can be answered by larger studies, including sufficient number of patients representing our daily clinical practice through comparing different levels of illness severity and duration of illness.

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