Original article

Initial response to active drug and placebo predicts outcome of antidepressant treatment

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Summary – In this study we tested whether initial clinical change (ICC) and initial subjective response (ISR) predict the outcome of antidepressant pharmacotherapy and whether ICC and ISR as predictors reflect specific pharmacological actions or a placebo effect. Forty patients with major depression were treated with three different antidepressants for 4 weeks. Overall clinical change and final subjective response were taken as outcome criteria. The patients were randomly assigned to two subgroups in a double-blind design. Initially, one group received the active drug and the other placebo. Afterwards, all patients were given the active drug. Significant correlations were found between ICC and ISR and at least one of the outcome criteria in the total sample and in each subgroup. The findings show that ICC and ISR may be significant predictors of outcome. The predictive value of ICC and ISR is not due to initial pharmacological effects, but to non-specific treatment factors.

initial response / antidepressants / prediction / outcome / depression

INTRODUCTION

In studies of the treatment of depression, tricyclic and tetracyclic antidepressants as well as MAO-inhibitors have been shown to be of significantly greater benefit to most patients than placebo treatment or no treatment at all (Klerman and Cole, 1965; Morris and Beck, 1974). However, not all depressed patients respond equally well to these forms of pharmacotherapy. Intensive research efforts have therefore been focused on the question as to how to predict whether a given treatment will have a relatively favorable or unfavorable outcome (Bielski and Friedel, 1976; Joyce and Paykel, 1989; Goodwin, 1993). While very few of the predictors reported in the literature have proven to have consistent predictive value, symptom change rated after 7 to 10 days of treatment has been suggested to have some predictive power (Woggon and Baumann, 1983; Woggon, 1988; Priebe, 1992). Woggon and Baumann (1983) concluded that "the course can be best predicted by the course itself".

In neuroleptic treatment of schizophrenics correlations have repeatedly been found between clinical change determined between 4 and 48 hours after application of a test dose (May et al, 1976) and clinical improvement after three or four weeks (May et al, 1980; May et al, 1981; Nedopil and Rüther, 1981; Nedopil et al, 1983; Bartkó et al, 1987). In addition to initial clinical change, the initial subjective response of patients has also been investigated in some studies and tested for its predictive value (Van Putten and May, 1978; Van Putten et al, 1980a; Van Putten et al, 1980b; Van Putten et al, 1981; Bartkó et al, 1987). Patients showing a dysphoric response and reporting a negative subjective effect after their first dose of a neuroleptic drug showed significantly less improvement during 4 weeks of treatment than did patients whose initial reactions were non-dysphoric (Singh and Smith, 1973; Singh, 1976; Singh and Kay, 1979).

Several authors (May and Goldberg, 1978; May et al, 1981; Priebe, 1992) have drawn attention to the problem that it has not been possible to esti-

mate to what extent initial clinical and subjective reactions are due to specific pharmacological factors and to what extent they reflect a placebo effect. May et al (1981) stressed the importance of conducting further studies to assess initial reactions to active drugs and to placebo and test their relationships with outcome.

In our own studies we have examined initial subjective reactions to complex treatment programs in groups of depressed and schizophrenic patients and found significant associations between these initial reactions and the course of symptoms during inpatient and day hospital treatment (Priebe, 1987; Priebe, 1992; Priebe and Gruyters, 1994; Bröker et al, 1995; Priebe and Gruyters, 1995). In patients receiving antidepressant medication some findings indicate that changes in psychopathological symptoms occurring during the first 7 to 10 days of treatment may predict outcome (Coryell et al, 1982; Fink et al, 1982; Katz et al, 1987; Kocsis, 1990; Nagayama et al, 1991). Fink et al (1982) published a study conducted in a heterogeneous sample of 33 patients, six of whom received tricyclic or tetracyclic antidepressants, and found an overall relationship between initial subjective response and outcome.

In this study we addressed two questions. Do initial clinical change (ICC) and initial subjective response (ISR) predict the outcome of antidepressant pharmacotherapy after 4 weeks? If ICC and ISR are predictors, do the ICC and ISR determined during placebo treatment also predict outcome of active drug treatment?

SUBJECTS AND METHODS

The study was carried out on all six wards of a 108-bed university psychiatric hospital (Department of Clinical Psychiatry, Freie Universität Berlin) in Berlin. We examined consecutively admitted patients with major depression according to DSM-III-R (American Psychiatric Association, 1987) who were to be treated with clomipramine, maprotiline or tranylcypromine. Informed consent was obtained from all patients; the study was approved by the ethics committee of the university hospital.

Forty-six patients were included in the study. Six patients dropped out for different reasons during the first few days. Thus, data from 40 patients (33 women, 7 men) were analyzed. The mean age was 49.5 years (SD = 16.8). Twenty-one patients were diagnosed according to DSM-III-R (American Psychiatric Association, 1987) as having recurrent major depression, 13 a single episode of major depression and six as being in a depressed episode of bipolar disorder. Twenty-three

patients had been admitted to a psychiatric hospital before, and 27 had been treated with antidepressant medication at some time in the past.

Before medication was instituted there was a minimum washout phase of 2 days. The decision as to which of the three antidepressants should be given and the dosage of the drugs was left entirely to the clinicians. The patients were randomly on a double-blind basis allocated to two groups. This allocation made a difference only for the first 48 hours of treatment. One group received the active drug from the start, while the other group received placebo for the first 2 days. After the first 48 hours each patient received the active drug.

All patients were treated for 4 weeks. Seventeen patients received clomipramine, 14 maprotiline and 9 tranylcypromine. On day 3, the first day on which the placebo subgroup was given the active drug, the mean doses were 65 mg clomipramine (SD = 19.9), 84 mg maprotiline (SD = 31.9) and 12 mg tranylcypromine (SD = 4.4). On day 28, the mean doses were 133 mg clomipramine (SD = 46.7), 150 mg maprotiline (SD = 19.6) and 20 mg tranylcypromine (SD = 8.7). In no case did psychiatrists or nurses on the wards express any doubts regarding the patients' compliance, and no patient experienced undue side effects during the treatment period.

Twenty patients in one subgroup received the active drug on the first two days, while the 20 patients in the other subgroup were given placebo. The two subgroups did not differ significantly on any sociodemographic or clinical variable recorded in this study.

The symptoms of depression were assessed on the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) by the psychiatrist on the ward. Ratings were made before the start of treatment, on day 2 (ie, after 48 hours), on day 4 (ie, after 96 hours) and after 28 days of treatment. The patients' subjective reactions were recorded on days 1, 2, 3 and 4 and 28 of treatment by an independent interviewer. They were assessed on a scale developed by Van Putten and May (1978). The interviewer was not informed about the clinician's rating of the patient's symptoms of depression, and the clinician was not informed about the patient's subjective response.

ICC was defined as the difference between the symptoms of depression as assessed on the HAMD between day 0 and days 2 and 4, respectively. Both differences were tested as predictors of outcome. Change in symptoms between days 0 and 28 was one of the two outcome criteria.

For the assessment of subjective response five questions were asked. Four of them were a German translation of the Van Putten and May scale. Because mood was assumed to be particularly relevant for antidepressant treatment we added the question: Does the medica-

S Priebe, M Bröker

Table I. Mean HAMD scores on day 0, 2, 4 and 28 for the total sample and the two subgroups.

Day	Total sample (n = 40)	Active drug subgroup (n = 20)	Placebo subgroup (n = 20)
0	19.2 ± 6.9	19.4 ± 6.4	19.1 ± 7.4
2	17.3 ± 7.8	17.3 ± 8.2	17.3 ± 7.5
4	15.8 ± 7.7	16.4 ± 8.0	15.2 ± 7.6
28	9.9 ± 7.0	10.1 ± 8.0	9.6 ± 6.1

Analysis of variance (ANOVA for repeated measures): factor time: $F = 35.07$, $df = 3, 114$, $P < 0.001$; factor group: $F = 0.01$, $df = 1, 38$, ns; interaction time X group: $F = 0.33$, $df = 3, 114$, ns.

Table II. Pearson's-correlations between initial clinical change (ICC) and initial subjective response (ISR) and overall change on the HAMD after 28 days for the total sample and the two subgroups.

	Total sample (n = 40)	Active drug subgroup (n = 20)	Placebo subgroup (n = 20)
ICC on day 2	0.48**	0.54**	0.47*
ICC on day 4	0.57***	0.65**	0.56**
ISR on days 1/2	0.39**	ns	0.65**
ISR on days 3/4	0.32*	0.39*	0.32+

$*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $+P = 0.09$ (correlations were tested one-tailed according to the hypothesized predictive relationship).

tion affect your mood? The answers were assessed on a visual analogue scale that was marked from −11 (extreme negative answer) to +11 (extreme positive answer), with 0 as the point of neutrality. Answers to all five questions were totaled and averaged. In further analyses, ratings made on day 1 and 2 were averaged to form a single score; the same procedure was applied to the ratings made on days 3 and 4. The ratings of final subjective response made on day 28 were taken as the second outcome criterion.

RESULTS

Predictors and outcome

Table I summarizes the mean HAMD scores for days 0, 2, 4 and 28 and shows statistical significance of changes over time and of differences between the subgroups.

Changes in symptoms over time were statistically significant. There were no significant differences between the two subgroups in regard to either the severity of the symptoms or the changes recorded over time.

ISR as measured on the Van Putten and May scale was slightly positive on days 1/2 (M = 0.64, SD = 2.6) and on days 3/4 (M = 0.19, SD = 2.6). The final subjective response on day 28 was significantly more positive (M = 2.5, SD = 4.3; t-test for paired samples: $t = 3.50$, $df = 39$, $P < 0.01$). There were no significant differences between the two subgroups as regards ISR on days 1/2 and 3/4, final subjective response or changes over time.

The ICCs recorded on days 2 and 4 were strongly correlated (Pearson's $r = 0.72$, N = 40, $P < 0.001$, tested two-tailed). There was also a significant correlation between ISRs recorded on days 1/2 and days 3/4 ($r = 0.67$, N = 40, $P < 0.001$). Significant correlations between ICC and ISR

were found in the placebo subgroup only (on day 2: $r = 0.56$, N = 20, $P < 0.05$, and on day 4: $r = 0.50$, N = 20, $P < 0.05$), and not in the active drug subgroup or in the total sample. There were no significant correlations between baseline HAMD scores and either the ICCs or the ISRs.

Prediction

Table II shows how ICC and ISR were correlated with overall clinical change in both the total sample and in the two subgroups.

Correlations between ICC and overall change on the HAMD were positive and similarly high in the total sample and in each subgroup. Patients whose symptoms had already diminished to a greater extent after 2 and 4 days showed significantly more improvement after 4 weeks. This applied even for the patients who were given placebo for the first 48 hours: the reduced severity of the symptoms of depression observed during placebo administration on the first two days of the treatment period predicted improvement during treatment with an active drug in the course of the next 26 days.

Correlations between ISR and overall clinical change were also positive. They were statistically significant for the total sample and partly in subgroups. Patients with a more positive ISR on days 1/2 and on days 3/4 tended to benefit more from the entire course of treatment than did those with more negative ISRs. Again, this result also applied to the placebo subgroup.

Table III summarizes the significant correlations between ICC and ISR respectively and final subjective response.

ISR proved to be a moderately good and significant predictor of final subjective response in each

Table III. Pearson's-correlations between initial clinical change (ICC) and initial subjective response (ISR) and final subjective response on day 28 for the total sample and the two subgroups.

	Total sample (n = 40)	Active drug subgroup (n = 20)	Placebo subgroup (n = 20)
ICC on day 2	ns	ns	0.40*
ICC on day 4	ns	ns	0.58**
ISR on days 1/2	0.57***	0.48*	0.68**
ISR on days 3/4	0.51**	0.39*	0.58**

$*P < 0.05$; $**P < 0.01$; $***P < 0.001$ (correlations were tested one-tailed according to the hypothesized predictive relationship).

subgroup and in the whole sample. ICC predicted final subjective response in the placebo subgroup only and not in the active drug subgroup or in the total sample.

In a next step we examined whether the predictive correlations shown in tables II and III were due to a third variable that influenced both predictors and outcome criteria in a similar way. None of the sociodemographic (gender, age, school education, professional qualification, marital and occupational status) or clinical (previous hospitalizations, previous treatments with antidepressants) variables was significantly correlated to ICC or ISR and one of the two outcome criteria. We thus failed to find a variable that explained the predictive correlations of ICC and ISR with outcome criteria as a third influencing factor.

Finally, two stepwise forward multiple regression analyses were calculated with overall clinical change and final subjective response as dependent variables. ICC on days 2 and 4 and ISR on days 1/2 and 3/4 were taken as independent variables. Because of the small size of the sample, these multivariate analyses were only done for the total sample and not for the two subgroups. In predicting overall change on the HAMD after 28 days of antidepressant medication, ICC on day 4 (Multiple regression: beta-weight = 0.57, N = 40, $P < 0.001$) and ISR on days 1/2 (beta-weight = 0.38, N = 40, $P < 0.01$) were included as predictors. The resulting multiple R was 0.70. The two predictors therefore explained 49% of the variance of overall clinical change. When final subjective response was taken as dependent variable, ISR on days 1/2 was the variable with the highest single correlation and its predictive power was not significantly improved by the inclusion of other predictors.

DISCUSSION

The reduction in depressive symptoms assessed after only 2 days, was significantly correlated with improvement after 4 weeks in this study. Thus, ICC may be valid as a predictor not only for neuroleptic treatment of schizophrenics, but also for antidepressant treatment. In addition to ICC, ISR was also tested as a predictor. Subjective response after 2 days predicted outcome and was significantly associated with both outcome criteria, ie, clinical change and subjective response after 4 weeks. This result is consistent with those of the study by Fink et al (1982). ICC and ISR have thus been found to be predictive of outcome in various forms of psychiatric treatment. However, whether this predictive relationship reflects the same underlying process in each form of treatment remains an open question. In this study the predictive correlation was not explained by the influence of a third variable. However, only basic variables were recorded and tested for their influence on both predictors and outcome criteria. In future studies, the question as to how the predictive value of ICC and ISR may be explained and mediated by the influence of other factors should be investigated in more detail.

Although the two predictor variables were assessed by simple methods and after only 2 and 4 days of treatment, their total predictive power explained almost half of the variance of eventual clinical improvement. The predictive powers of ICC and ISR seem to be separate and partly independent from each other.

The predictive values of ICC and ISR were different for the two subgroups and depended on whether they were assessed on day 2 or day 4. However, these differences were not statistically significant and should not be interpreted. The only findings that should be interpreted are that ICC and ISR predicted overall clinical change, that ISR predicted final subjective response, that these results applied to both subgroups, and that ICC and ISR together predicted more variance in overall clinical change. Interpretation of these findings should take into account methodological shortcomings of the study, most of which are due to the naturalistic aspects of its approach. The sample was small and somewhat heterogeneous, and the patients received different doses of three different antidepressants. Before the findings have been replicated in similar or different settings and particularly in groups with more severe depression, they should be interpreted cautiously and it remains unclear to what extent they can be generalized.

The design of the study enabled us to test the influence of specific pharmacological factors during the first two days, but not during the following four weeks when all patients were on active drug. ICC and ISR were similar, regardless of whether they reflected reactions to placebo or to active drug. Eventual clinical outcome did not differ between the two subgroups either: patients who received placebo during the first two days and active drug during the following 26 days, showed a similar improvement of symptoms as the patients did who received active drug throughout the full 28 days. ICC and ISR predicted eventual outcome of active drug treatment in both subgroups, regardless of whether patients received active drug or placebo during the first two days. Initial reactions as well as final improvement might be spontaneous, reflect a placebo effect or be due to other non-specific factors. Non-specific treatment factors that already exert an influence during the initial stages of treatment may remain influential during the following 4 weeks and interact with specific treatment effects. Both this influence and the interaction may account for the portion of the variance in final improvement that was predicted. The way in which non-specific and specific factors interact has been a subject of interest to researchers for several decades but still remains widely unclarified (Rickels, 1968; Brody, 1980; Joyce, 1989; Rothschild and Quitkin, 1992).

If replicated, these findings will have certain consequences for research and clinical practice. Investigations on the processes involved in antidepressant drug therapy should examine ICC and ISR more systematically. In clinical practice, patients' statements as to how they perceive the effect of an antidepressant should be of interest, even when they are made after only two days of treatment. When the ICC is rather unfavorable and the ISR more negative than positive, interventions aimed at changing non-specific treatment components may be considered.

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