

PREDICTION OF OUTCOME IN SCHIZOPHRENIA USING THE SUBJECTIVE RESPONSE TO A TEST DOSE OF A NEUROLEPTIC

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SUMMARY

Twenty four patients meeting R.D.C. criteria for schizophrenia were assessed using the B.P.R.S. before starting neuroleptics. They were then given a standardized test dose of haloperidol. Their subjective response to the test dose was assessed 4 hours later by a blind rater. The B.P.R.S. ratings were repeated after 3 weeks of neuroleptic treatment. A dysphoric response to the test dose was associated with a poor therapeutic outcome. The implications of these findings are discussed.

There is considerable evidence to show that neuroleptic drugs are effective in the treatment of schizophrenia. However some patients do not respond well to drug treatment. Many efforts have been made to predict as to which patients will improve with treatment (Langfeldt, 1969; Itil et al., 1975; Seeman, 1985). No approach has been uniformly successful. Singh and Smith (1973) made an interesting observation that patients who became 'high and happy' after starting haloperidol (euphoric responders) improved more with drug treatment than those who became 'anxious, tense and depressed' (dysphoric responders). These earlier findings were later confirmed by Singh (1976) in a study on 18 schizophrenic patients. Dysphoric reactions to neuroleptics were measured on a 7 point scale. Most patients with a significant dysphoric response did not respond well to treatment.

Similar findings were also reported by May et al. (1976). Subjects were given a test dose and the subjective response was measured 4 hours later. The subjective response varied from highly negative to highly positive and correlated significantly with the clinical improvement ($p < 0.001$).

This work was extended further by Van Putten and May (1978). They observed 42 newly admitted schizophrenic patients without drugs for 3-5 days. All were then given 2.2 mg/kg body weight of chlorpromazine. The subjective response was measured 4 hours later by a blind rater using a standardized questionnaire. The outcome was rated using the B.P.R.S. Sixty percent of patients had an euphoric response and 40% had dysphoric response to the test dose. A significant correlation was seen between the subjective response & clinical improvement. Dysphoric responses were associated with a worse outcome.

Similar findings have been reported by workers from other countries, such as Canada (Hogan et al, 1985) and Hungary (Bartko et al., 1987). To the best of our knowledge no study of this nature has been done on Indian patients. This study aims to test the hypothesis that the subjective response to a test dose of a neuroleptic can be used to predict the response to treatment in a group of Indian schizophrenic patients.

Material and Methods

This study was performed in the Central Institute of Psychiatry, Ranchi

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from February to May, 1988. Thirty consecutive schizophrenic patients, meeting the inclusion criteria, who were admitted to the institute were taken up for the study. The inclusion criteria were :

- (a) R.D.C. criteria (Spitzer et al., 1975) for schizophrenia.
- (b) Off drugs for atleast 2 weeks before admission.
- (c) Cooperative and gave consent for the study.

Patients who had been given only 1 or 2 doses of drugs before admission were kept drug free in the ward for 3 days and were then taken up for the study. The patients were assessed using the B.P.R.S. (Overall and Gorham, 1962) soon after admission, before they received any drugs. All the ratings were done by the first author. The patients were then given a standardized test dose of haloperidol (0.05 mg/kg of body weight). The drug was given in a liquid form making exact titration of the dose possible.

Four hours after the test dose, the subjective response was assessed, using the standardized questionnaire of Van Putten and May (1978), by an independent blind rater who was not involved in the rest of the study. This consisted of 4 questions :

- (1) How does this medication agree with you?
 - unpleasant or bad effect.
 - pleasant, good or helpful effect.
- (2) Did it make you feel calmer?
- (3) Did it affect your thinking?
- (4) Do you think that this would be the right medication for you?

Each question was scored on a scale ranging from +11 for a maximal positive response, 0 for no effect, to -11 for a maximal negative response. The subjective response questionnaires were sealed after completion and were opened only after the entire study had been completed. The patients were started on haloperidol after assessment of the subjective response.

Male patients received 20 mg/day and female patients received 15 mg/day. The resident incharges of the patients were requested not to change the doses unless it was absolutely necessary. Anti-parkinsonian drugs were given if required. None of the patients received E.C.T.

The patients were re-assessed using the B.P.R.S. 3 weeks after starting neuroleptics. The change in scores was noted. The subjective responses were analyzed after all the B.P.R.S. ratings were completed. Those with a total subjective response score less than or equal to 0 were classified as dysphoric responders. Those with a score greater than 0 were classified as syntonic responders.

Results

Thirty patients (24 males and 6 females) were taken up for the study. Six male patients had to be dropped from the study for the following reasons :

- (a) 3 patients were discharged before completion of the study.
- (b) 1 patient's diagnosis was revised due to new findings.
- (c) 1 patient developed a physical illness.
- (d) 1 patient later refused to cooperate for the study.

Of the remaining 24 patients left in the study, 5 had a dysphoric response to the test dose and 19 had a syntonic response. These 2 groups did not differ significantly from each other with respect to age, duration of illness, initial B.P.R.S. scores or sex distribution (Table I). However, the reduction in B.P.R.S. scores with treatment was significantly less in the dysphoric group ($p < 0.05$).

Taking the entire sample ($n = 24$), the Pearson correlation coefficient between the subjective response scores and the change in the B.P.R.S. scores was highly significant ($r = 0.57$, $p < 0.005$). The correlation between the duration of illness and the change in B.P.R.S. scores was also

TABLE 1—*Comparison of the Syntonic and Dysphoric Groups*

	Dysphoric group (n=5)		Syntonic group (n=19)		't'	Significance
	Mean	S.D.	Mean	S.D.		
Mean age (in years)	28.8	11.01	31.05	6.28	0.60	N.S.
Mean length of illness (in years)	4.2	4.13	4.82	3.44	0.35	N.S.
Mean initial B.P.R.S. score	30.80	12.44	35.84	7.24	1.19	N.S.
Mean change in B.P.R.S. score	5.8	7.12	15.95	11.12	1.92	p<0.05
Sex distribution	4 males 1 female		14 males 5 females			Not significant

d.f. =22

significant ($r=0.36$, $p<0.05$).

There were no significant correlations between:

- The subjective response scores and the initial B.P.R.S. scores.
- The change in B.P.R.S. scores and the current age or the age of onset of the illness.
- The initial and final B.P.R.S. scores.

There was no difference in the outcome between male and female patients.

Discussion

In this study, 5 (20.8%) patients had a dysphoric response to the test dose and 19 (79.2%) had a syntonic response. The dysphoric and syntonic patients did not differ with respect to age, duration of illness, severity of psychopathology or sex distribution—(Table I). However, the improvement with drug treatment was significantly less in the dysphoric group. Furthermore, the correlation between the subjective response scores and the change in B.P.R.S. scores for the whole sample was highly significant ($r=0.57$, $p<0.005$, $n=24$). This indicates a very strong relationship between a positive response to the test dose and clinical improvement. The only other significant correlation was between the length of illness and improve-

ment, a longer duration of illness being associated with a poorer outcome ($r=-0.36$, $p<0.05$).

It is interesting that the most significant predictor of poor outcome in this study was found to be a dysphoric response to the test dose. The findings of this study are similar to those of earlier studies in the Western literature (Van Putten and May, 1978; Hogan *et al.*, 1985; Bartko *et al.*, 1987). The subjective response could not be predicted on the basis of clinical and demographic variables, and it was not related to the severity of psychopathology (Initial B.P.R.S. scores). A dysphoric response was strongly associated with a poor outcome.

The relationship between the subjective response and the improvement with treatment has been shown to be independent of the type of neuroleptic used. Similar findings have been reported with haloperidol (Singh and Smith, 1973; Bartko *et al.*, 1987) and with chlorpromazine or thiothixene (Van Putten *et al.*, 1980a). No correlation has been found between the plasma level of the drug and the subjective response (Van Putten *et al.*, 1980b).

Van Putten *et al.* (1981) reported an association between dysphoric responses

and later development of extrapyramidal side effects of neuroleptics. However these findings were not confirmed by Hogan et al. (1985). The subjective responses appears to be an idiosyncratic phenomenon, due to either altered receptor sensitivity or a patient's personal interpretation of the effects of the drug (Van Putten et al., 1980b).

We ask schizophrenic patients many questions but we rarely ask them whether their medication agrees with them. This study suggests that we could learn a lot from their answer to this simple question.

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