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Does Propranolol have an Antipsychotic Effect?
A Placebo-Controlled Study in Acute Schizophrenia

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Thirty-six acute schizophrenics were randomly assigned to dextro (d)-propranolol or placebo in a double blind trial lasting four weeks. All patients had a fixed dose of haloperidol during the first week, which resulted in an initial improvement in both groups. Thereafter, a deterioration towards base-line was seen. Six patients on placebo, but none on propranolol were treatment failures at the end of three weeks ($P<0.001$). Comparison of change in scores from week 2 to 4 showed significantly greater deterioration in the placebo group; d-propranolol thus had a better effect than placebo in sustaining the initial improvement with haloperidol. The overall magnitude of clinical change from pre-treatment scores is small, the majority of the patients showing little or no overall improvement. It is concluded that d-propranolol has a detectable therapeutic effect, which by inference must have a novel pharmacological basis, but this is not as potent as standard neuroleptics.

The need to discover compounds which have potent antipsychotic effects but are different from conventional neuroleptics in their mode of action and associated side-effects continues. Of the several drugs investigated during the last decade, propranolol, a beta adrenoreceptor blocker, has received wide attention. The evidence in favour of an antipsychotic effect has ranged from empirical clinical observation (Atsmon & Blum, 1970) to uncontrolled trials (Atsmon *et al*, 1971; Yorkston *et al*, 1974; 1976; Sheppard, 1979, Hanssen *et al*, 1980) and more recent controlled studies. Of the controlled studies, some have supported such a claim (Yorkston *et al*, 1977; Lindstrom & Persson, 1980; Pugh *et al*, 1983), whereas others have failed to substantiate it (Myers *et al*, 1981; King *et al*, 1980; Peet *et al*, 1981a). The double-blind studies have, however, been conducted on chronic schizophrenics, and propranolol has been used as an adjunct to ongoing neuroleptic therapy in almost all the studies, apart from those by King *et al*, (1980) and Peet *et al* (1981a). The only controlled study carried out in acute schizophrenics compared propranolol with chlorpromazine (Yorkston *et al*, 1981), but did not have a placebo control.

The beneficial effects of propranolol in schizophrenia has been reported in its conventional racemic (d-l) form. Dextro (d)-propranolol, which is almost devoid of beta-adrenergic blocking activity (Shanks, 1976) and hence easier to use, was first investigated by us in an uncontrolled pilot study (Hirsch *et al*, 1981), and we reported that there was a definite improvement in seven out of nine schizophrenic patients. Interestingly, d-propranolol has no known effects on dopaminergic (Creese *et al*, 1978) or serotoninergic (Green & Graham-Smith, 1976) systems. Furthermore, psychological measures of habituation showed improvement with both (d-l) and d-propranolol consistent with the effect seen with conventional neuroleptics (Gruzelier *et al*, 1979). It was, therefore, thought that a double-blind placebo controlled study in acute schizophrenic patients would be directly relevant to the core question—does propranolol have antipsychotic activity?

Method

Sample

The sample consisted of recently admitted psychiatric inpatients suffering from acute or acute-on-chronic schizophrenia with florid delusions and/or hallucinations. The diagnosis of schizophrenia was arrived at independently by two psychiatrists and the patients were scrutinised by a structured interview, the Present State Examination (PSE) (Wing *et al*, 1974). Those patients who had received long acting neuroleptics in the last three weeks or oral medication in the last 10 days were not included. Patients with marked physical illness, in particular, any cardio-respiratory condition, organic cerebral disease, established history of alcoholism or drug abuse were excluded from the study. Detailed physical examination and investigations were carried out in every case. All patients and their nearest relative, where applicable, consented to participate in the study.

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Treatment plan

After 3–7 days observation, patients were treated double blind for four weeks with identical capsules of d-propranolol or placebo (ICI Ltd). The trial medication was started with 40 mg qid with daily increments (except on weekends) of 160 mg. This increase was regulated by the patients' clinical state, response to treatment and his pulse and blood pressure before each dose. Pulse rate below 60/minute and/or blood pressure below 90/60 mm Hg necessiated missing that dose. All patients received haloperidol 5 mg bd with an anticholinergic, procyclidine 5 mg tds, during the first week of the trial only. This modification had to be made after a very poor recruitment of acute patients to the trial during the first eight months since neither d-propranolol nor placebo provided the sedation necessary to settle acute patients when first admitted. Also, a clinical judgement was made at the end of third week to decide whether a patient should go on to the fourth week based on improvement up to that time, and the urgency to ensure adequate treatment. If the patient was dropped from the study because of lack of improvement, end-point ratings were made at that time. After patients were discontinued or completed 3 or 4 weeks in the trial they were started on haloperidol 10–20 mgs per day for 4 weeks (in some cases higher doses) and reassessed 4 weeks later.

Assessment procedure

The psychiatric condition of the patients was evaluated by using the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and Manchester Scale (MS) (Krawiecka *et al*, 1977). These scales were administered at week 0, 1, 2 and 4 (or at the time of drop-out). On the BPRS the scores consisted of Total Score, Thought Disorder Score (sum of the scores of Conceptual disorganisation, Hallucinatory behaviour, Unusual thought content) and Non-Thought Disorder score (sum of Blunted affect, Emotional withdrawal, Suspiciousness, Grandiosity, Mannerisms or posturing, Hostility and Motor retardation). Thought disorder and Non-Thought Disorder scores together constitute the Schizophrenia Score. The rest of the items on the BPRS constitute the Non-Schizophrenia Score. The scores on the MS consisted of Total Score, Positive Score (sum of Delusions, Hallucinations and Thought disorder and Incongruity of affect), Negative Score (sum of Poverty of speech, Blunted affect) and Non-specific Score (sum of Anxiety, Depression and Motor retardation). In addition patients were rated pre and post trial by a Nurses Rating Scale used by us in a previous study (Manchanda & Hirsch, 1981). A change in the global severity of illness (worse, unchanged, mild, moderate, marked improvement, and recovered) was recorded at the end of the trial and after four weeks on conventional neuroleptic (haloperidol) given post trial.

Results

Forty-six newly admitted patients with an acute or acute on chronic episode of schizophrenia consented to participate in the trial during a period of 30 months; ten patients, however, refused medication during the first week, and therefore were not entered into the trial. Random allocation resulted in an equal number of patients in the d-propranolol ($n=18$) and placebo group ($n=18$). Patients' socio-demographic and clinical characteristics are shown in Table I. There was no statistical difference between the two groups on any measure. Also, there was no difference (using Mann Whitney Test) between the d-propranolol and placebo groups in the pretreatment total scores and subscores on the BPRS and MS.

Although no patient had received long-acting depot neuroleptics within three weeks of starting the trial, one patient in the propranolol group and five in the placebo group had been on long-acting neuroleptics in the previous year to starting the trial. The patient in the propranolol group had the last injection (fluphenazine decanoate 25 mgm) 6 weeks before entering the trial. Of the patients in the placebo group, 3 had discontinued it 10–12 months before entering the trial. The remaining two had received their injections (fluphenazine decanoate 12.5 mgm and depixol 40 mgm) 6 weeks previously. Thus, the difference in depot medication preceding the trial is only one patient in the placebo group receiving 12.5 mgm of fluphenazine decanoate, and this would tend to bias the results against propranolol.

The maximum dose in the d-propranolol group ranged between 800–1760 mg/day mean 14010 mg/day) and in the placebo group the number of capsules prescribed was comparable to 1120–2080 mg/day (mean 1562 mg/day) of propranolol. The number of days taken to reach the maximum dose was 15.5 and 17 respectively. Six patients on placebo, compared to none in the propranolol group, were treatment failures at the end of three weeks ($P<0.001$), and two patients (one in each group) were dropped out at $2\frac{1}{2}$ weeks as they became suicidal. Figs. 1 and 2 show the change in mean Total score (week by week) on the BPRS and on the MS. Figs. 3 and 4 show the change in mean subscores on these two scales.

Not unexpectedly, the scores in both groups (Figs. 1–4) reduced markedly by the end of one week, as all patients received haloperidol. Also, there was a significant reduction between pre- and post-treatment scores in the propranolol group on The Thought Disorder ($P=0.01$), Schizophrenia ($P=0.01$) and Total ($P=0.02$) Scores of the BPRS as well as on the Positive ($P=0.03$) and Non-Scientific ($P=0.04$) score of the Manchester Scale (MS). However, a between-group comparison of the change in scores at the end of the trial (week 0 minus week 4 rating for each group, including drop-outs at week 3) showed that the propranolol group was not significantly different from the placebo group (using Mann Whitney/Wilcoxon Rank Sum Test) in measures of Total score as well as various sub-scores on the BPRS and the MS. The change in score for each item on the BPRS ($n=19$) and MS ($n=9$) was also calculated. Only one item (Blunted Affect) on both scales distinguishes the two groups, those on d-propranolol significantly better than placebo ($P<0.05$).

The percentage change in Total and Schizophrenia subscore of BPRS and MS showed that majority of the patients in both d-propranolol (10/18) and placebo group (13/18)

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TABLE I
Socio demographic and clinical variables in trial groups

	d-Propranolol (n=18)	*Placebo (n=18)*
Sex M	10	8
Age (mean and range)	32.3 (18–55)	33.2 (20–58)
Age at onset (Mean and range)	27 (18–45)	28 (16–56)
No. of previous admissions		
Nil	7	3
1–4	10	14
NK	1	1
Episodes treated (Mean and range)	2.6 (1–5)	3 (1–7)
Most recent illness		
No previous episode	6	2
Within 6 months	10	14
6–12 months	2	2
Catego subclasses		
Nuclear schizophrenia	7	7
Catatonic schizophrenia	2	5
Paranoid psychoses	3	3
Affective psychoses	3	1
Schizophrenia without FRS	2	2
Borderline psychoses	1	—

None of the differences between the scores in each group were statistically significant.

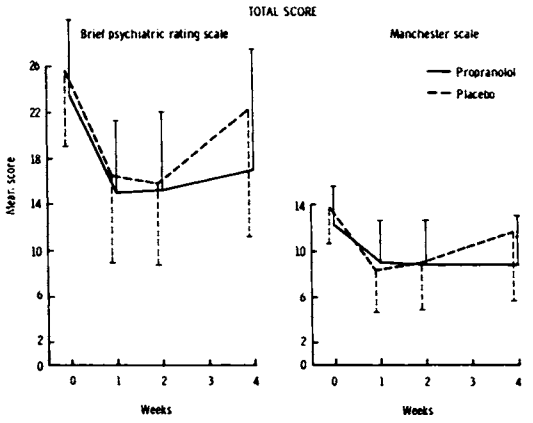


FIG. 1. The mean changes in total scores in the propranolol and placebo groups on the BPRS and MS over 4 weeks are shown. The vertical line equals one standard deviation. There was a significant difference in the Total Score in the propranolol group as measured on the BPRS [23.3 [wk. 0] vs 17.1 [wk. 4], $P=0.02$] but not on the MS [12.2 & 8.8 respectively]. The findings on the BPRS was not significant when compared with the placebo group [25.6 [wk. 0], 22.2 [wk. 4]]. Between wk. 2 to 4, significantly greater deterioration [$P<0.05$] was seen in the placebo [wk. 2 mean score = 15.9 [BPRS], 9.1 [MS]] as compared to the propranolol group [wk. 2 mean score = 15.2 [BPRS], 8.9 [MS]]

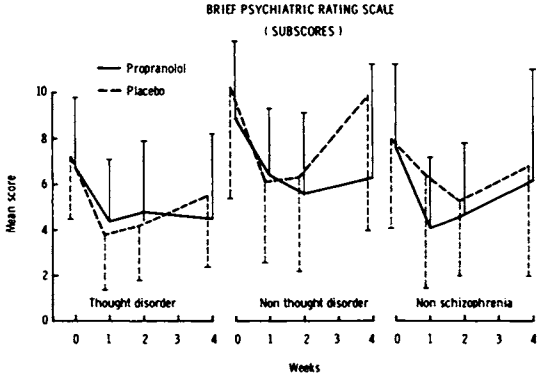


FIG. 2. The mean changes in BPRS sub-scores are shown. A significant reduction [$P=0.01$] was seen in the propranolol group on Thought Disorder subscore [6.8 [wk. 0] vs 4.5 [wk. 4]], but the finding was not significant when compared to the placebo group [7.2 [wk. 0], 5.5 [wk. 4]]. Between week 2 and 4 the improvement was maintained on Thought Disorder subscore and there was less deterioration on Non-Thought Disorder sub-score in the propranolol group, compared to placebo group [$P<0.05$]. There was no difference in the Non-Schizophrenia sub-score.

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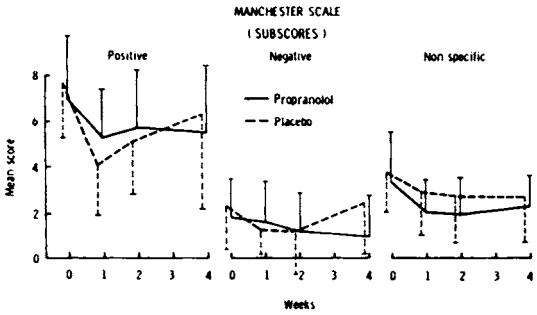


FIG. 3 Shows the change in mean subscore on the MS. There was a significant reduction [$P<0.05$] in the Positive [7.0 [wk. 0] vs. 5.5 [wk. 4]] and non specific subscores [3.3 [wk. 0] vs. 1.9 [wk. 4]] in the propranolol group but the finding is not significant when compared to the placebo group. Between week 2 and 4 there is a significant difference [$P<0.05$] between propranolol and placebo groups in the Positive and Negative subscores but not in the Non Specific subscore.

showed less than 25% improvement at the end of the trial (see Tables II & III). Comparisons of these findings for d-propranolol and placebo group were not significant using the chi square test. There was no significant change in either group in the Nurses' rating carried out before and at the end of the trial. None of the patients in the d-propranolol group had a major side-effect or hypotension necessitating discontinuation of the trial. Side-effects when reported (in both groups) were minor, and did not require any intervention.

Indication of anti-psychotic effect

There were, however, some novel findings, Firstly, seven patients in the placebo group, compared to only one in the propranolol group, could not complete the 4-week trial. Secondly, although the overall clinical effect is small, discontinuing haloperidol after one week was followed by significantly greater deterioration in the placebo group, as compared to the propranolol group (Figs. 1–4), suggesting a pharmacological effect for propranolol. A comparison between the two groups of the change in scores from the end of week 2 (one week after discontinuing haloperidol) to the end of the trial showed significant difference on the sub-scores of Thought Disorder ($P=0.04$), Non-Thought Disorder ($P=0.04$) and Total score ($P=0.03$) of the BPRS as well as on the Positive ($P=0.04$), Negative ($P=0.04$) and Total score of the MS ($P=0.02$) but the findings were not significant for the Non-Schizophrenia score ($P=0.66$) of BPRS and Non-Specific score of MS ($P=0.54$). Thus, there appears to be a specific effect on schizophrenic symptomatology. The finding that the overall clinical effect is small is further supported by Table IV. It shows that on a global scale, majority of the patients in both

TABLE II
Percentage change in total score

	<25%		*25–50%*		*51–75%*		*>75%*	
	BPRS	*MS*	*BPRS*	*MS*	*BPRS*	*MS*	*BPRS*	*MS*
Propranolol ($n=18$)	10	9	3	7	2	1	3	1
Placebo ($n=18$)	13	10	2	5	2	2	1	1

$x^2=1.5913$ DF = 3 NS
$x^2=0.719298$ DF = 3 NS

TABLE III
Percentage change in schizophrenia score

	<25%		*25–50%*		*51–75%*		*>75%*	
	BPRS	*MS*	*BPRS*	*MS*	*BPRS*	*MS*	*BPRS*	*MS*
Propranolol ($n=18$)	9	9	1	6	5	1	3	2
Placebo ($n=18$)	11	10	3	5	2	3	2	—

$x^2=2.68571$ DF = 3 NS
$x^2=3.14354$ DF = 3 NS
In both tables the percentage change in Total Score and Schizophrenia Score on The Brief Psychiatric Rating Scale (BPRS) and Manchester Scale (MS) are shown. Percent change in score = Baseline Score − Final Score/Baseline Score × 100 Schizophrenia score on the BPRS is the sum of Thought Disorder and Non Thought Disorder Subscores and on the MS it is the sum of Positive and Negative subscores. The end point score of 6 patients on placebo who were treatment failures at 3 weeks, and 2 (one in each group) who were dropped out at 2½ weeks because they were suicidal are included.

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TABLE IV
Global change

	Propranolol (end of trial)	*Placebo*	*Haloperidol (4 wks. post trial)*
Completely remitted	2	2	4
Marked improvement	1	0	8
Moderate improvement	3	2	17
Mild improvement	1	2	4
Unchanged	8	6	2
Worsened	3	6	0
	18	18	35

$x^2 = 22.1955$ DF = 2 $P < 0.001$
(Mod.—complete rem. vs Mild-unchanged)
One patient was lost in the follow-up.

groups were unchanged or deteriorated (11 of 18 on d-propranolol and 12 of 18 on placebo) by the end of the trial. The group as a whole was treatment-responsive, as suggested by the improvement in both groups during the initial one week of treatment with haloperidol. Further, open treatment with haloperidol from weeks 5–8 resulted in moderate or better improvement in 29 out of 35 patients, as compared to the propranolol and placebo groups, wherein only six and four patients respectively showed a similar global improvement ($P < 0.001$), see Table IV).

Discussion

This is the first placebo-controlled trial to evaluate the efficacy of propranolol in acute schizophrenia. Given the inconsistency between several research findings which found that propranolol has an antipsychotic effect and others which failed to find an effect, we had set out to answer the fundamental question of whether or not propranolol has an antipsychotic action. The two groups matched on sociodemographic variables, clinical characteristics, and pretreatment scores, and eventually proved responsive to a conventional neuroleptic, haloperidol.

In terms of clinical efficacy, this study failed to show an appreciable effect for d-propranolol in the treatment of acute schizophrenia. The majority of the patients in both groups showed less than 25% improvement on Schizophrenia score of the BPRS and the MS. Also, a large number of patients on d-propranolol ($n = 11$) or placebo ($n = 12$) were globally unchanged or worse at the end of the trial and two patients in each group had remitted. A between-group comparison found that the change in scores of the propranolol group was not significantly different from the placebo group over the trial period. This result is consistent with the only other controlled study on acute schizophrenics, that of Yorkston *et al.* (1981), who were unable to find a significant overall difference between propranolol and chlorpromazine. Like our study, no significant difference was found between the two groups in either the Thought Disorder or Non-Thought disorder sub-score of the BPRS. Although there wasn't a placebo group, it is noteworthy that the mean peak dose of chlorpromazine was only 300 mg. At this dose, chlorpromazine has not been found to be better than placebo in 9 out of 26 trials (Davis & Garver, 1978). Also, when the change in score of individual items was considered, Yorkston *et al* found significantly less reduction in conceptual disorganisation for patients treated with propranolol. The effect of propranolol was modest, and half of the patients on propranolol showed minimal or no improvement.

The present study, however, showed a significant pharmacological effect of d-propranolol, when compared to placebo: d-Propranolol had a small but discernable effect in sustaining the improvement obtained from one week of treatment with haloperidol. Statistically, there was a difference between the d-propranolol and placebo groups on the change in scores between week 2 and 4, the placebo group having deteriorated significantly more on various sub-scores of the BPRS and the MS (Figs. 1–4, see Results). Both positive and negative symptom scores deteriorated more on placebo than propranolol. What is the explanation for such an effect? Is it possible that d-propranolol sustained or stabilised the beneficial effect of haloperidol observed during the first week of combined treatment? Peet *et al* (1981b) showed that there is a pharmacokinetic interaction between chlorpromazine and propranolol, resulting

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TABLE V
Plasma haloperidol levels

	Week 2	*Week 4*
D-Propranolol	0.49* ($n=6$)	0.16 ($n=6$)
Placebo	0.23 ($n=9$)	0.10 ($n=4$)

Table V shows the mean plasma haloperidol levels (estimated by extracted haloperidol radioimmuno assay) for a subsample of trial patients. *Comparatively higher value because of 1 patient. The mean taking out this extreme value was 0.24 ng/ml.

in higher levels of chlorpromazine sulfoxide in patients receiving a combined treatment, but there is no evidence to generalise the statement to include other neuroleptics such as haloperidol. In any case, a sub-group of patients in this trial had haloperidol assays, but the levels in both groups at week 2 (<0.5 ng/ml) and at week 4 (<0.16 ng/ml) were far below the expected therapeutic levels of haloperidol (>5.0 ng/ml) and therefore of no clinical significance (Table V).

Some double-blind placebo-controlled studies on chronic patients have failed to find any advantage for propranolol over placebo (Peet *et al*, 1981a; King *et al*, 1980). However, a recent controlled study by Puch *et al* (1983) showed that propranolol was more effective than placebo. Although this study was in chronic schizophrenics on concommitant neuroleptics, all patients had florid symptoms as an inclusion criterion. The observed change was, however, not so great as reported in earlier uncontrolled studies. Improvement was observed on the 'irritability' sub-score of a nurses' rating scale, the NOSIE (Honigfeld & Klett, 1965). The change on schizophrenia sub-score of the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg *et al*, 1978) just reached a significance level ($P=0.046$) and that at the end of 8 weeks. No significant change was observed on the BPRS. We have argued elsewhere (Manchanda and Hirsch, 1984) that the schizophrenia scale of CPRS has a bias in including only those items which are sensitive to change over time and not necessarily with treatment alone. Further, given the large number of analyses attempted, the observed level of significance in the absence of other significant results cannot be regarded as a definitive finding for a clinical effect of propranolol in the treatment of schizophrenia.

The present double-blind study was initiated because of the encouraging preliminary results with d-propranolol and the ease in using it on account of minimal beta-blocking activity. However, could it be that the racemic (d-l) propranolol and not the dextro(d)-propranolol has a clinical antipsychotic effect? Moller *et al* (1979) used (d) and (d-l) propranolol in six manic patients, and found that an anti-manic action is exerted by both preparations of propranolol. Based on this study and findings from a previous study (Emrich *et al*, 1979), they concluded that the anti-manic effect of d-propranolol (dose range 2000–3000 mg/day) is on average about half that of (d-l) propranolol. Although the dose of d-propranolol used in the present study (800–1760 mg/day) is lower than the above study, studies using 400–900 mg of (d-1) isomer have also reported a positive effect (Yorkston *et al*, 1974), 1977, Pugh *et al*, 1983). Thus, the lack of a clinical antipyschotic effect is observed, despite using adequate dosage in the present study.

This trial highlights once again the need for double-blind studies to confirm the positive effects observed in an uncontrolled study such as ours (Hirsch *et al*, 1981). Alternatively, it is recommended that the criteria for measuring change in uncontrolled studies should be stricter, such that improvement should be based on at least 75% change in score. Re-analysis of our uncontrolled study on these criteria results in an improvement in two or at the most three out of nine patients. This result is more consistent with the findings on the present controlled study.

In conclusion, it appears that d-propranolol has a pharmacological effect on schizophrenic symptomatology which is evident on rating scales, but this effect does not compare favourably with conventional neuroleptics as a clinical agent. Of particular interest is the effect seen in the negative symptoms of schizophrenia—symptoms which generally do not respond to currently available neuroleptics. The findings in this study should be of interest to neuropharmacologists because they point to the possibility that d-propranolol, a non-neuroleptic agent with no known effects on the beta-adrenergic, dopaminergic or serotoninergic system, has a specific pharmacological effect on the positive as well as negative symptoms of schizophrenia which is not associated with an improvement in the non-specific symptoms. Whether or not propranolol can be modified to produce a more effective anti-psychotic effect provides a challenge to the pharmaceutical industry which we hope will be taken up.

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