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A Double-Blind Comparison of Melperone and Thiothixene in Psychotic Women Using a New Rating Scale, the CPRS

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Summary. Eighty-one women with psychosis of schizophrenic and paranoid type were assigned to a double-blind study comparing the clinical effects of melperone (100 mg × 3) and thiothixene (10 mg × 3). The antipsychotic effect was evaluated by clinical rating according to the CPRS and the NOSIE-30 scales before and after 2 and 4 weeks of drug treatment. A satisfactory inter-rater reliability was obtained for the CPRS. Significant correlation was also found between the CPRS and NOSIE ratings.

Treatment with both drugs was associated with significant reductions in morbidity as estimated by several measures of therapeutic effect from the CPRS, by the NOSIE scale and by global ratings. There were no marked differences at any rating time point between the drugs in this regard. There were more extrapyramidal side effects in the thiothixene group than in the melperone-treated patients.

The results encourage the use and further evaluation of melperone in the treatment of psychotic patients.

Key words: Schizophrenia – Neuroleptic drugs – Psychiatric evaluation – Rating scales – Melperone – Thiothixene.

Introduction

Despite recent advances in psychopharmacology, the treatment of psychotic patients is still far from optimal. Several patients fail to benefit from drug treatment (Bleuler, 1972). Neuroleptic drugs also have side effects, some of which are severe and sometimes irreversible, as the tardive dyskinesias (Crane, 1977). Therefore an intensified search for better drugs and alternative treatment modalities in psychosis is required.

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The development of new antipsychotic drugs with low frequency of side effects would represent progress in this direction. In order to develop such compounds, further refinement of the available clinical research methodology would be of value.

Recently, a comprehensive psychopathology rating scale (CPRS) has been constructed, covering most signs and symptoms in psychosis (Åsberg et al., 1978). Each item and the scoring levels of this scale are described in detail in order to increase the precision of the ratings.

One aim of this study was to examine the reliability and usefulness of some clinical rating devices for the examination of psychotic patients being treated with potential therapeutic drugs. We were interested in evaluating the CPRS and its relationship with a nurses' rating scale (NOSIE-30). A modified version of the Simpson and Angus (1970) scale for side effects was also evaluated. The second aim of the study was to compare the effectiveness of two antipsychotic drugs on groups of psychotic patients who were repeatedly evaluated by these rating scales. Melperone and thiothixene were the two compounds.

Melperone, a butyrophenone derivative, has been reported to exhibit neuroleptic effects in animal behavioral tests (Christensen et al., 1965) as well as antipsychotic properties in man (Schulsinger et al., 1965; Haugen, 1967; Gross and Haberler, 1970; Walcher, 1970). In two studies with melperone on schizophrenic patients (Schulsinger et al., 1965; Haugen, 1967), chlorpromazine was used as a reference compound. No difference in therapeutic or side effects was found between the two drugs. Melperone has also been compared with promazine and haloperidol in senile psychoses; again there were no differences between the effects of the drugs (Engstrand, 1967; Nørgård et al., 1967; Härnryd et al., 1974). Some of the above-mentioned studies have indicated a low frequency of extrapyramidal and other side effects in melperone-treated patients. In these studies, however, small inhomogeneous patient groups have been used; reliability and validity of the ratings were not examined. Therefore the clinical evidence for an antipsychotic effect of melperone in psychosis and, specifically, in schizophrenia is still ambiguous. For this reason the present study of melperone was undertaken.

Thiothixene, a thioxanthene derivative, was selected as reference compound, since its clinical profile as regards autonomic and extrapyramidal side effects is similar to that of the butyrophenones. Thiothixene induces neuroleptic effects in animal behavioral tests (Weissman, 1974). It has antipsychotic properties in schizophrenic patients (Bishop et al., 1966; Gallant et al., 1966; Kellam and Jones, 1971; Burnett et al., 1975; Jacobsson et al., 1976).

The study was performed as part of an investigation aiming at analyzing the relations between clinical and biochemical effects in drug-treated psychotic patients. In this paper the clinical effects of melperone and thiothixene are reported.

Materials and Methods

The protocol for the study was approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden. Eighty-one acutely admitted psychotic women (age range 19—63) were selected from the emergency ward. All of these patients exhibited symptoms that satisfied WHO

diagnostic criteria for schizophrenic or paranoid type psychosis (World Health Organization, 1973). In the present study the following narrower set of criteria was selected from these:

Inclusion Criteria. Presence of thought disorder, delusions, and/or auditory hallucinations.

Exclusion Criteria. Presence of organic brain disorder, somatic disease, alcohol and drug abuse, manic or depressive psychosis, or borderline symptomatology.

Routine physical examination showed all patients to be somatically healthy.

Of the patients (thiothixene = 9, melperone = 11), 20 had received single doses of different antipsychotic drugs during the month preceding the study. No patient received neuroleptics within the last 48 h before the beginning of the study. There was no significant difference between the treatment groups in this regard. From the 81 patients admitted, 17 dropped out for various reasons (e.g., refusal of medication or lumbar puncture). The number of 'dropouts' did not differ between the treatment groups. The 64 remaining patients completed the study according to the protocol. The data presented in this paper pertain exclusively to these 64.

Administration of Drugs

During an initial period lasting 2—7 days, placebo tablets were administered. During this time, the clinical condition was rated and blood and lumbar cerebrospinal fluid (CSF) samples were taken. After the placebo period, tablets containing melperone (Buronil 100 mg) or thiothixene (Navane 10 mg) were administered according to a double-blind procedure. The double-dummy technique was used. During the first week, one placebo tablet and one tablet of active compound (original preparation) were given at 8 a.m. and at 4 p.m. After this week, the dose was increased to three tablets per day of the active compound with the additional tablet given at 12 a.m. These doses (melperone 100 mg × 3, thiothixene 10 mg × 3) were kept constant during the rest of the study. The clinical condition was rated again, and blood and CSF samples were taken at 2 and 4 weeks after the start of treatment.

Additional Medication

Twenty-one patients (melperone = 9, thiothixene = 12) received diazepam (Stesolid, AB Dumex, Sweden) for sleep induction or sedation. All these patients were prescribed diazepam during active neuroleptic treatment and five of them also during the placebo period. Fifteen patients (melperone = 4, thiothixene = 11) were also given biperiden (Akineton, AB Meda, Sweden, 5 mg × 3) after the appearance of severe extrapyramidal symptoms. Treatment with diazepam and biperiden did not significantly influence the therapeutic effects. Thus the scores of therapeutic improvement for a restricted group of patients, excluding those that received these drugs, did not produce results different from that of the whole group. Therefore the results from those patients receiving the additional medication were pooled with the data from those who strictly followed the protocol.

A. Ratings of Psychopathology

1. Each patient was rated by two psychiatrists (L.B. and C.H.) using the CPRS (Table 1). The ratings were based on an interview lasting about 45 min. Both psychiatrists were present at the interview and alternated in interviewing the patients. Previous rating protocols were not available at the later interviews. Ratings were performed after the interview according to seven-point scales (range 0—3). The mean of the scores from the two raters were used for the evaluation of treatment effects. High scores on an item correspond to a pronounced psychopathology. According to the construction of the CPRS, scores between 0 and 1 represent variants of normal behavior.

2. In addition to the CPRS, an unstructured global rating of psychosis was made in order to give the raters' total impression of the patient's degree of psychopathology (Cronholm et al., 1974). This also was scored according to a seven-point scale.

Table 1A. Ratings of reported CPRS item in 81 unmedicated psychotic women. Interrater reliability, mean score, and frequency of patients with scores ≥1. Items are ranked according to frequency

CPRS item (No.)	Interrater reliability *r*	Mean score	Frequency % ≥1
Ideas of reference and persecution (10)	0.77	1.69	84
Disrupted thoughts (12)	0.79	1.40	70
Concentration difficulties (17)	0.97	0.88	51
Illusions and hallucinations (14)	0.82	0.90	50
Reduced sleep (25)	0.98	0.79	45
Inner tension (4)	0.94	0.88	44
Pessimistic thoughts (8)	0.94	0.78	43
Autonomic disturbances (27)	0.90	0.77	41
Depersonalization (21)	0.92	0.75	39
Reduced sexual interest (30)	0.98	0.80	38
Hostile feelings (5)	0.88	0.58	33
Passivity feelings and inertia (15)	0.88	0.63	33
Sadness (2)	0.97	0.57	31
Worrying over trifles (3)	0.83	0.57	31
Compulsive thoughts (13)	0.83	0.56	29
Reduced appetite (26)	0.95	0.55	29
Fatiguability (16)	0.92	0.54	28
Ideas of grandeur (7)	0.94	0.60	27
Indecision (18)	0.97	0.51	27
Derealization and perception difficulties (22)	0.89	0.41	26
Inability to feel (20)	0.68	0.54	24
Muscular tension (28)	0.96	0.34	21
Phobias (32)	0.90	0.36	19
Hypochondriasis (9)	0.81	0.36	18
Failing memory (19)	0.84	0.27	17
Conversion symptoms (31)	0.92	0.25	16
Disorientation (23)	0.90	0.31	15
Morbid jealousy (11)	0.95	0.25	13
Suicidal thoughts (34)	0.96	0.23	13
Elation (1)	0.93	0.15	10
Increased sexual interest (29)	1.00	0.15	9
Rituals (33)	0.88	0.15	9
Ecstatic experiences (6)	0.96	0.17	8
Increased sleep (24)	1.00	0.12	5

All coefficients are significant ($P < 0.001$) and calculated according to Spearman's rank correlation test

Table 1B. Ratings of observed CPRS item in 81 unmedicated psychotic women. Interrater reliability, mean score, and frequency of patients with scores ≥ 1. Items are ranked according to frequency

CPRS item (No.)	Interrater reliability r	Mean score	Frequency % ≥ 1
Incongruity of affect (45)	0.83	0.69	43
Incoherent speech (51)	0.77	0.84	39
Blunted affect (43)	0.73	0.51	28
Withdrawal (38)	0.77	0.63	27
Perseveration (54)	0.69	0.52	27
Slowness of movement (56)	0.76	0.50	25
Hallucinatory behavior (62)	0.69	0.45	20
Flight of ideas (53)	0.66	0.38	20
Pressure of speech (46)	0.62	0.33	16
Reduced speech (48)	0.76	0.36	16
Muscular tension (58)	0.45	0.30	16
Apparent sadness (40)	0.80	0.40	13
Faint voice (49)	0.78	0.27	13
Agitation (57)	0.63	0.31	13
Perplexity (36)	0.38	0.28	11
Hostility (41)	0.63	0.23	11
Distractability (37)	0.47	0.20	10
Emotional overflow (44)	0.46	0.31	10
Blank spells (52)	0.70	0.22	10
Elated mood (39)	0.65	0.13	6
Overactivity (55)	0.47	0.15	6
Autonomic disturbances (61)	0.61	0.15	6
Mannerisms and postures (60)	0.80	0.11	5
Loudness (47)	0.50	0.07	3
Involuntary movements (59)	0.82	0.06	3
Labile emotional response (42)	0.21	0.07	2
Sleepiness (35)	0.48	0.04	0
Specific speech defects (50)	—	0.00	0

All coefficients besides that for item 42 are significant ($P < 0.001$)

3. The patient's clinical condition was also rated according to the Nurse's Observation Scale for Inpatient Evaluation (NOSIE-30; Honigfeld et al., 1966). A specially trained research nurse performed these ratings.

B. Ratings of Side Effects

At the time of the CPRS interview, observed and reported side effects were rated according to a modification of the Simpson and Angus (1970) scale for extrapyramidal symptoms (Tables 6 and 8). Here also, each item was rated according to a seven-point scale (range 0—3).

All the ratings of psychopathology were performed during the placebo period (R_0), after 2 (R_2) and 4 (R_4) weeks of treatment with the active compounds. Side effects were rated at R_2 and R_4.

Results

CPRS Ratings

In Table 1 the interrater reliability calculated as the Spearman's rank correlation coefficient for the score of the two raters at R_0 is presented for all the items. Generally high reliability is obtained. All the coefficients with one exception (item 42) are highly significant.

The items were ranked according to the percentage of patients having a score of 1.0 or higher (Table 1). As expected, there was high rank correlation between the mean of the pretreatment score and the percentage frequency of the item ($r = 0.98$). Items with a high frequency in the group were selected for the estimation of the severity of the psychotic condition and the effect of treatment.

Three item combinations were selected on the basis of (1) item frequency in the patient group studied, (2) the mean value of the scores, and (3) the relation of their content to Bleuler's criteria of schizophrenia (Tables 1 and 2). $\Sigma 3_{Rep}$ is based on the reported items that had the highest mean scores in the group. These items are related closely to the inclusion criteria. Thus their high frequency in the group was expected. $\Sigma 7_{Rep}$ represents a broader item combination, where besides the six

Table 2. Five measures of psychotic morbidity derived from the CPRS

CPRS item No.		$\Sigma 3_{Rep}$	$\Sigma 7_{Rep}$	$\Sigma 3_{Obs}$	$\Sigma 6$	$\Sigma 10$
4	Inner tension		×			×
10	Ideas of reference and persecution	×	×		×	×
12	Disrupted thoughts	×	×		×	×
14	Illusions and hallucinations	×	×		×	×
17	Concentration difficulties		×			×
18	Indecision		×			×
25	Reduced sleep		×			×
38	Withdrawal			×	×	×
45	Incongruity of affect			×	×	×
51	Incoherent speech			×	×	×

Table 3. Interrater reliability for the CPRS combinations and the global score

Measure	R_0	R_2	R_4	$R_0 - R_4$
$\Sigma 3_{Rep}$	0.88	0.92	0.88	0.85
$\Sigma 3_{Obs}$	0.86	0.73	0.44	0.79
$\Sigma 6$	0.90	0.92	0.71	0.85
$\Sigma 7_{Rep}$	0.98	0.95	0.90	0.95
$\Sigma 10$	0.96	0.95	0.82	0.94
Global score	0.71	0.87	0.82	0.68

All the coefficients are significant ($P < 0.001$)

items with the highest frequencies, another one from Bleuler's criteria, the item Indecision (18), was included, since this item also showed high frequency in another group of psychotic patients (Wode-Helgodt et al., 1978). $\Sigma 3_{Obs}$ is based on the observed items that had the highest frequencies.

$\Sigma 6$ represents the sum of $\Sigma 3_{Rep}$ and $\Sigma 3_{Obs}$. The six items included in this combination are all considered typical of schizophrenia (Bleuler, 1911) and should reflect the severity of schizophrenic symptomatology.

The sum of $\Sigma 7_{Rep}$ and $\Sigma 3_{Obs}$, $\Sigma 10$, represents an even wider combination of items related to schizophrenic psychosis.

The scores on these item combinations were calculated for each patient. There was good interrater reliability for each combination before and during treatment. There was also high reliability for the difference in item combination scores between $R_0 - R_4$ (Table 3).

Therapeutic Effect

There were no significant differences between the two treatment groups at R_0 on any of the CPRS items. The scores of most CPRS items and all the item combinations selected as typical for schizophrenia were significantly reduced by both drugs already after 2 weeks of treatment (Wilcoxon's signed-rank test) (Fig. 1 and Table 4). Additional reduction occurred between the second and fourth week of

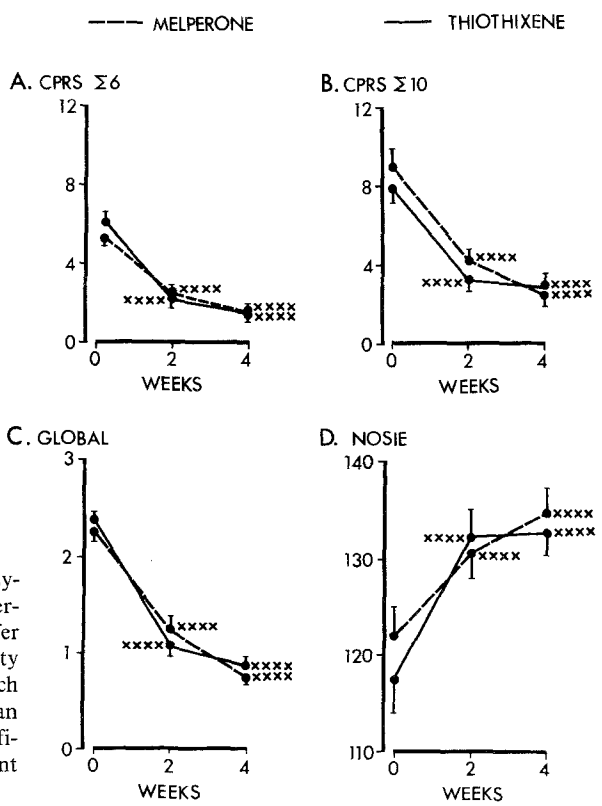

Fig. 1A–D. Morbidity scores in psychotic women treated with melperone or thiothixene. **A, B, C, D** refer to the different psychotic morbidity measures described in the text. Each point on the figure refers to mean value ±SE. **** indicates significant difference from pretreatment levels, $P < 0.001$

Table 4. Mean scores in 10 CPRS items and CPRS combinations in relation to drug treatment

Item No.	Melperone group; Mean values			Comparisons			Thiothixene group; Mean values			Comparisons		
	R_0	R_2	R_4	R_0-R_2	R_2-R_4	R_0-R_4	R_0	R_2	R_4	R_0-R_2	R_2-R_4	R_0-R_4
4	1.03	0.74	0.21	—	****	****	0.75	0.28	0.19	***	—	****
10	1.66	0.68	0.52	****	—	****	1.72	0.56	0.40	****	—	****
12	1.38	0.79	0.58	****	*	****	1.41	0.57	0.41	****	—	****
14	0.68	0.31	0.14	***	—	****	1.08	0.32	0.17	****	—	****
17	0.99	0.42	0.38	**	—	***	0.78	0.41	0.41	**	—	—
18	0.58	0.16	0.21	**	—	**	0.45	0.15	0.21	—	—	—
25	0.94	0.31	0.16	****	—	****	0.66	0.49	0.41	—	—	—
38	0.44	0.30	0.14	—	***	***	0.79	0.24	0.20	****	—	****
45	0.67	0.25	0.12	****	*	****	0.75	0.33	0.18	***	—	****
51	0.76	0.17	0.05	****	—	****	0.90	0.37	0.24	****	—	****
$\Sigma 3_{Rep}$	3.65	1.82	1.24	****	**	****	4.06	1.43	0.99	****	**	****
$\Sigma 3_{Obs}$	1.78	0.72	0.31	****	****	****	2.32	0.88	0.62	****	*	****
$\Sigma 7_{Rep}$	7.23	3.52	2.21	****	**	****	6.28	2.58	2.21	****	—	****

*: $P<0.05$; **: $P<0.025$; ***: $P<0.01$; ****: $P<0.001$

treatment for some items. This seemed to be more marked in the melperone group. For no item combination was there any significant difference between the melperone and the thiothixene groups.

To compare group differences for single items, a covariance analysis was performed where scores were adjusted for differences in pretreatment levels (May, 1968; Klein et al., 1975; Lehman, 1975). Only for two items, Incoherent speech (51) and Reduced sleep (25), were there significant differences between the groups. Thus at R_4 the melperone-treated patients had shown greater improvement on Incoherent speech (51) than those treated with thiothixene ($P < 0.025$). This was most pronounced among patients with a high score at R_0 (interaction $P < 0.001$). The melperone group demonstrated greater improvement on Reduced sleep (25) than the thiothixene group ($P < 0.05$).

A few items, which were not included in the combinations, demonstrated significant differences between the groups at R_4. Thus the melperone group showed greater improvement ($P < 0.05$) on the following items: Flight of ideas (53), Slowness of movement (56), observed Muscular tension (58), and Autonomic disturbances (61).

Only for two items, Increased sleep (24) in both groups, and reported Muscular tension (28) in the thiothixene group, was there significant deterioration at R_4.

In order to detect any specific effect profiles for the drugs, the improvements in the individual CPRS items of Σ 10 were analyzed using a stepwise discriminant analysis (Wilk's method, Overall and Klett, 1972). This procedure did not result in the construction of clinically relevant clusters of items.

Global Ratings

There was high interrater reliability for the global ratings generally (Table 3). There were also high correlations between the global ratings and the scores obtained in the different CPRS combinations (Table 5). At R_0 the two treatment groups differed with regard to the global rating. Thus seven patients in the thio-

Table 5. Correlations between the different measures of psychotic morbidity

A.		$\Sigma 3_{Rep}$	$\Sigma 3_{Obs}$	$\Sigma 6$	$\Sigma 7_{Rep}$	$\Sigma 10$
R_0	Global	0.63	0.61	0.79	0.54	0.65
R_2	Global	0.77	0.64	0.84	0.69	0.76
R_4	Global	0.79	0.46	0.80	0.70	0.75

All the coefficients are significant ($P < 0.001$)

B.		$\Sigma 3_{Rep}$	$\Sigma 3_{Obs}$	$\Sigma 6$	$\Sigma 7_{Rep}$	$\Sigma 10$	Global
R_0	NOSIE	−0.30**	−0.37***	−0.34***	−0.07	−0.14	−0.44****
R_2	NOSIE	−0.29**	−0.34***	−0.33***	−0.29**	−0.30**	−0.46****
R_4	NOSIE	−0.33***	−0.32***	−0.40****	−0.41****	−0.44****	−0.50****

*: $P < 0.05$; **: $P < 0.025$; ***: $P < 0.01$; ****: $P < 0.001$

All correlation coefficients are calculated according to Spearman's rank correlation test

thixene and only one in the melperone group reached the maximal global score, 3.0. However, the median was the same and the mean global scores did not differ significantly between the two groups. The covariance analysis used adjusted for the difference between the groups at R_0. In both treatment groups there was a significant reduction of the global score after 2 as well as 4 weeks (Fig. 1). Neither at R_2 nor R_4 was there any significant difference between the treatment groups.

NOSIE Ratings

Significant but low correlations were obtained between the scores of the NOSIE ratings, some of the CPRS combinations, and the global ratings (Table 5). The correlations are negative, since a low score in the NOSIE reflects a pronounced severity of psychopathology. The scores of the NOSIE ratings did not differ significantly between the treatment groups at any one of the three ratings (Fig. 1). In both treatment groups there were highly significant changes in the scores, indicating marked improvements.

Side Effects

Interrater reliability was only calculated for the first three observed items of the scale because of the low frequency obtained in the other items. For these three items there was high interrater reliability (Table 6). The classical parkinsonian side effects reflected in the first three items of the scale were studied as $\Sigma\, 3_p$. At 2 weeks there were significantly more extrapyramidal side effects ($\Sigma\, 3_p$) ($P < 0.05$) in the thiothixene group than in the melperone group (Table 7). At this time, three patients in the melperone group and four in the thiothixene group were treated with biperiden. At R_4 there was no difference with regard to extrapyramidal side effects ($\Sigma\, 3_p$) between the treatment groups. However, at this time, four patients in the melperone and 11 in the thiothixene group received biperiden. This difference in antiparkinson medication is not significant.

The distribution of reported side effects with a symptom intensity greater than 1.0 in the treatment groups is listed in Table 8. Ten patients in the melperone and

Table 6. Rating of observed side effects

No.	Observed items	Interrater reliability correlation coefficient	
		R_2	R_4
1	Gait	0.82	0.81
2	Elbow rigidity	0.73	0.67
3	Tremor	0.67	0.70
4	Dystonia		
5	Akathisia		
6	Hypersalivation		
	$\Sigma\, 3_p$	0.85	0.77

All coefficients are significant at $P < 0.001$

Table 7. Distribution of extrapyramidal side effects ($\Sigma 3_p$) at 2 weeks[a]

Scores on $\Sigma 3_p$	Number of patients	
	Melperone	Thiothixene
4—9	0	1
3—4	1	1
2—3	1	6
1—2	2	8
0—1	24	17

The distributions differ significantly ($P < 0.05$ Mann-Whitney U-test)

[a] One patient on melperone and two on thiothixene were not rated for side effects

Table 8. Rating of reported side effects

No.	Side effect	Weeks	Melperone		Thiothixene	
			Frequency of patients (%)	M	Frequency of patients (%)	M
7	Somnolence	2	39	1.75	21	1.73
		4	39	1.70	25	1.64
8	Muscular tension	2	7	1.00	3	2.30
		4	4	2.00	12	1.63
9	Tremor	2	7	1.40	9	1.50
		4	4	1.50	9	1.67
10	Dry mouth	2	11	1.17	3	1.00
		4	7	1.75	0	—
11	Salivation	2	0	—	0	—
		4	0	—	12	1.75
12	Constipation	2	0	—	6	1.65
		4	4	1.00	3	2.00
13	Micturition disturbance	2	0	—	3	1.30
		4	4	2.00	0	—
18	Blurred vision	2	14	1.78	3	1.50
		4	18	1.58	6	2.00
21	Vertigo	2	0	—	6	1.75
		4	7	1.00	3	1.00
22	Akathisia	2	4	2.00	6	1.50
		4	4	1.30	9	1.50

The frequency and mean values represent data from patients with scores ≥ 1.0

13 in the thiothixene group did not report side effects. Among the reported items, Somnolence (7) was most frequent. For none of the reported side effects was there any significant difference between the treatment groups. However, Increased salivation (11) and Muscular tension (8) were commonly reported during thiothixene treatment, whereas Blurred vision (18) appeared to be more frequent in the melperone group. The appearance of Blurred vision and Dry mouth in the melperone group was unexpected, since animal studies indicate that melperone lacks anticholinergic effects (Olsson et al., 1977).

Discussion

The CPRS (Åsberg et al., 1978) is a new rating scale that has not previously been evaluated regarding its applicability for the measurement of psychopathology in drug-treated psychotic patients. This was done in this study by applying the CPRS to a group of psychotic women. By analyzing data before and during drug treatment, the scale could be evaluated for the estimation of 'present status' as well as 'change' in relation to treatment.

Reliability of Ratings

For each rating and the changes in ratings occurring during treatment, satisfactory reliabilities were obtained in practically all the items and the item combinations (see below). The present type of meticulous reliability data presentation is required in treatment evaluation studies to give the reader information about the precision of rating data.

Validity of Ratings

The definition of psychosis differs between various psychiatric schools. To circumvent this controversy, explicit inclusion and exclusion criteria selected from those used in the International Pilot study of Schizophrenia (WHO, 1973) were used in this study in order to define our concept of schizophrenic and paranoid type of psychosis. The criteria were related to Bleuler's (1911) primary and secondary symptoms of schizophrenic psychosis. Thus all the patients had manifest thought disorder, delusions, and/or auditory hallucinations.

The CPRS was constructed for the rating of different types of psychopathological conditions including psychoses. Several items in the scale were specifically defined to cover generally accepted clinical signs and symptoms of schizophrenic psychosis. The CPRS item combinations used for therapeutic evaluation in this study (Table 2) were selected on the basis of frequency of occurrence and rank order of mean intensity for each item in the examined group of psychotic women. In an independent study on another group of psychotic patients using the same procedure, very similar item combinations were obtained from the CPRS ratings (Wode-Helgodt et al., 1978). On the other hand, the rating of depressive patients with the CPRS (Montgomery and Åsberg, 1978; Fyrö et al., 1979) gave completely different item combinations as did also the rating of healthy volunteers

selected on the basis of lack of psychiatric history (Wode-Helgodt et al., 1978). All these data suggest that the CPRS is a sensitive rating scale that discriminates among psychotic, depressive, and normal human behavior. The usefulness of the CPRS for the rating of psychosis was further confirmed in the present study by its correlation with another commonly used rating scale for ward personnel (NOSIE-30; Honigfeld et al., 1966) (Table 5). The latter scale has been used extensively for the evaluation of therapeutic effects in drug-treated psychotic patients (Clark et al., 1971; Pinard et al., 1972). The fact that the correlation coefficients were fairly low may be partly due to the different item compositions of the two scales. The NOSIE includes items related to social competence, an area not covered by the CPRS.

One of the drugs in this study, thiothixene, has previously been shown to have antipsychotic properties (Bishop et al., 1966; Gallant et al., 1966; Kellam and Jones, 1971; Burnett et al., 1975; Jacobsson et al., 1976). Using the CPRS we found a marked reduction of the morbidity scores during thiothixene treatment. These results supply pharmacological evidence for the view that the CPRS is a sensitive indicator of treatment-related changes in psychosis.

In summary, the methodological part of the present study demonstrated a high interrater reliability for the CPRS in psychotic patients. Moreover, the CPRS was shown to be a useful rating instrument for estimation of psychosis and for evaluation of treatment-related changes.

Therapeutic Effects of Melperone and Thiothixene

The two drugs studied in this investigations were administered in fixed doses that were selected on the basis of previous clinical studies in psychotic patients (Schulsinger et al., 1965; Bishop et al., 1966; Gallant et al., 1966; Haugen, 1967; Gross and Haberler, 1970; Walcher, 1970; Kellam and Jones, 1971; Burnett et al., 1975; Jacobsson et al., 1976). The doses used were thought to be optimal for the average psychotic patient.

During treatment with both drugs, marked improvements were seen in morbidity as measured by the CPRS, the NOSIE, and the global ratings. There was no marked difference between the drugs in this regard. Possibly, the therapeutic effect occurred earlier during thiothixene than melperone treatment.

Since this study employed fairly large numbers of patients, about 30 per treatment group, and used three different raters for the evaluation of treatment effects, the statistical procedures used were thought to have power to distinguish between two drugs with different profiles (Overall et al., 1967). Accordingly, the fact that no consistent differences were obtained between the two drugs may indicate that the doses selected are roughly equipotent regarding antipsychotic effect.

In any type of treatment evaluation specific as well as nonspecific effects operate. Examples of nonspecific effects are the spontaneous course of the disorder, psychotherapeutic influence from the staff, and general environmental factors. Both treatment groups should have been similarly affected by these nonspecific factors in the present study. The reduction of the morbidity score should be due to the combined effect of pharmacological and nonspecific influences. If the nonspecific factors play a major part in the treatment effect, a small difference between the drugs tested may be obscured by the substantial

influence from these nonspecific factors. Accordingly, the present data do not exclude the possibility that significant, albeit small, differences may exist between melperone and thiothixene regarding antipsychotic effect.

Side Effects

Side effect evaluation demonstrated that extrapyramidal symptoms can be scored with high interrater reliability.

The classical extrapyramidal symptoms initially occurred with lower frequency in the melperone-treated patients compared with those receiving thiothixene. More thiothixene-treated patients were also treated with biperiden in the later part of the study. The difference between the two drugs regarding extrapyramidal symptoms is in accordance with biochemical data previously reported from the same study. Thus thiothixene compared with melperone caused significantly greater elevations of the HVA content in lumbar CSF and of prolactin concentrations in CSF and plasma (Bjerkenstedt et al., 1977a and b). These results supply clinical and biochemical evidence for a relationship between blockade of central dopamine receptors and extrapyramidal symptoms.

In summary, the present study indicated that melperone has antipsychotic properties that are not inferior to those of thiothixene, a well-documented antipsychotic drug. Melperone had a lower frequency of extrapyramidal side effects, which may be related to its fairly weak dopamine receptor blocking potency. The properties of melperone demonstrated in the present study recommend its further evaluation and use in the treatment of schizophrenic and paranoid psychosis.

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