Among the clinical side effects, extrapyramidal symptoms occurred in a high percentage of the cases, while one patient had a cerebral seizure and another vomited repeatedly during the trial period. Considering this and our findings it would appear that Majeptil has a value comparable to that of other phenothiazines in the treatment of this group of schizophrenics. (Additional information: our psychophysical studies with a single dose (10 mgs.) of Majeptil revealed that the drug dampens sensory input and motor output; these results being comparable to the effect of the other phenothiazine drugs.)

Opinion: Therapeutic in chronic schizophrenics.

(Ban, T.A., Papathomopoulos, E. and Schwarz, L. Clinical Studies with Thioproperazine (Majeptil). Comprehensive Psychiatry, 3:284-291, October 1962).

II. (3) Early Drug Evaluation with MK-240 in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested an antidepressant effect of this substance.)

This 6-week study was carried out with 15 of our chronic mental patients, selected on the basis of the chronicity of their illness, inadequate response to previous therapies, prevailing withdrawal, apathy, and/or depressive mood change.

Our procedure was based on clinical observations and a battery of tests and examinations: laboratory (except transaminase); physical; the Verdun Side Effect Check List; the Verdun Target Symptom and Depression Rating Scales were regularly completed.

Medication was administered in 15 mgs. daily in 3 divided doses.

The general impression gained by the ward staff during this trial was that patients on the drug appeared to be more active, less withdrawn, less depressed, but some were rather euphoric. The ward personnel was pleased with the effects of the drug in about 50% of the cases and enquired about the possibility of keeping these improved patients on the medication after termination of the trial. These changes were also expressed on the rating scales of the total group, with 8 presenting decreased scores on the Depression and Target Symptom Rating Scales. The remaining 7 were unchanged on the Depression Rating Scale while on the Target Symptom Scale, 5 remained unchanged and 2 became aggravated. The improvement was manifested on the two scales in the following areas: mood, facial expression, retardation, expected social response. The aggravation was due to an increase in excitement and anxiety.

5 of the 15 cases had to be taken off medication because of adverse effects. The first patient was taken off the drug trial shortly after the beginning of administration because of behavioral toxicity

(excitement, anxiety), the second after 22 days because of orthostatic hypotension, the third on the 30th day because of bradycardia, the fourth on the 32nd day because of behavioral toxicity (excitement, anxiety) and the fifth on the 35th day because of the occurrence of haemorrhagic urticaria.

Because of the occurrence of haemorrhagic urticaria, platelet counts were determined at the end of the 5th week on 10 of these patients. Only 1 showed a definitely normal value (280,000), 2 were borderline (191,000 and 189,000), and the 7 others were below 175,000, 1 of them having a value of 61,000. Platelet count determinations were completed again in 14 cases one week later which revealed one case in the normal range (250,000) 1 borderline (175,000), all the others below 175,000 and 3 below 100,000. (Additional information: human toxicity study conducted later with 5 patients did not confirm the thrombocytopenic effect.)

Opinion: Therapeutic in chronic depressions. Thrombocytopenia needs to be confirmed.

II. (4) Early Drug Evaluation with MP-809 in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested antidepressant properties of this compound.)

An uncontrolled clinical trial was carried out over a period of 6 weeks with 15 patients selected from different chronic units of the hospital. Patients for this study were selected on the basis of the chronicity of their illness, depressive mood change, inadequate response to previous therapies, prevailing withdrawal and/or apathy.

In addition to our clinical observations, the following tests were conducted: laboratory; physical; and the usual testing by the Verdum Target Symptom and Depression Rating Scales.

Medication was administered from 15 to 60 mgs. daily in gradually increasing doses.

On the Depression Rating Scale improvement was seen in 4 of the 7 items in the following order: mood, facial expression, retardation and depressive ideation. The sum of the total score of the Depression Rating scale decreased in this experiment (mean: 4.93 to 3.64).

In analysis of the individual cases, of 15 patients, 10 (66.6%) improved, 1 showed no change and 4 became worse. Behavioral toxicity of the drug was mild and was manifested in these 4 cases in the increased scores on the Target Symptom Rating Scale, in symptoms of increased excitement and suspiciousness.

None of the 15 patients was taken off medication because of clinical side effects. No physical toxicity was observed. In 4 of the patients the antidepressant effect of the drug was thought by the ward personnel to be superior to previously applied treatment.

Opinion: Therapeutic in chronic depressions.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit I. Canadian Psychiatric Association Journal. In Press.)

II. (5) Early Drug Evaluation with Nozinan in Chronic Psychiatric Patients.

(Pre-clinical and early clinical trials suggested anti-psychotic and antidepressant properties of this compound.)

An uncontrolled clinical trial was carried out over a period of 10 weeks with 20 patients from a chronic unit of the hospital. Patients were selected on the basis of chronicity of illness and having a depressive syndrome as their prominent clinical feature. The group was subdivided into the following categories: schizo-affective disorder 6; manic-depressive psychosis 4; involutional melancholia 5; neurotic depressive reaction 5.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory (except transaminase); physical; the Verdun Side Effect Check List and Depression Rating Scale were administered.

Treatment usually began with an oral dosage schedule of 15 mgs. daily in three divided doses, usually increased after a few days, at first to 30 mgs. daily and thereafter to higher doses ranging from 75 to 150 mgs.

As the baseline, the total score was taken of the Depression Rating Scale obtained before commencement of therapy. A 75 to 100% reduction of this score was considered equivalent to a remission, and classified as 'excellent'; a 50 to 75% reduction was rated a good improvement, and classified as 'good'; and a 25 to 50% reduction equivalent to a partial or temporary improvement, and classified as 'fair'. A reduction of the score of less than 25% was considered as 'failure' of therapy.

The results obtained according to the rating scale are seen in Table XIV.

	Excellent	Good	Fair	Failure	Total
Schizoaffective	1	4	1	0	6
Manic-Depressive	0	2	1	1	4
Involutional Melancholia	1	3	1	0	5
Neurotic Depressive Reaction	0	1	1	3	5
Total	2	10	4	4	20

Table XIV

Reduction of the score was observable in clinical assessment within 2 weeks of commencement of the therapy. The greatest improvement in our sample occurred between the 4th and 8th weeks. At the end of the 8th week, rating score was approximately the same as at the end of the drug trial.

A further breakdown according to diagnostic categories shows that the best results were observed in patients diagnosed as having schizoaffective disorders and involutional melancholia. There was no failure of therapy in these groups. Patients with a diagnosis of neurotic-depressive reaction responded less favorably and four-fifth of this group did not improve. (Additional information: our psychophysical studies with single doses (25 mgs.) of Mozinan revealed that the drug dampens sensory input and motor output, as is the case with other phenothiazine drugs.)

Opinion: Therapeutic in chronic depressions.

(Ban, T.A. and Schwarz, L. Systematic Studies with Levomepromazine (Mozinan).
Journal of Neuropsychiatry. In Press.)

II. (6) Early Drug Evaluation with Sordinol in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested antipsychotic effect of this substance.)

An uncontrolled clinical trial was carried out over 10 weeks with 20 chronic patients. They were selected on the basis of chronicity of their illness, inadequate response to previous therapies and prevailing symptoms in the area of mental integration.

Evaluation was based on clinical observations and on a battery of tests and examinations: laboratory (except transaminase); physical; psychological: Word Association Time (Table XV) and

Conformity Index (Table XVI) from the Verdun Projective Battery, and the Verdun Side Effect Check List and Symptomatological Check List (Table XVII) completed at regular intervals.

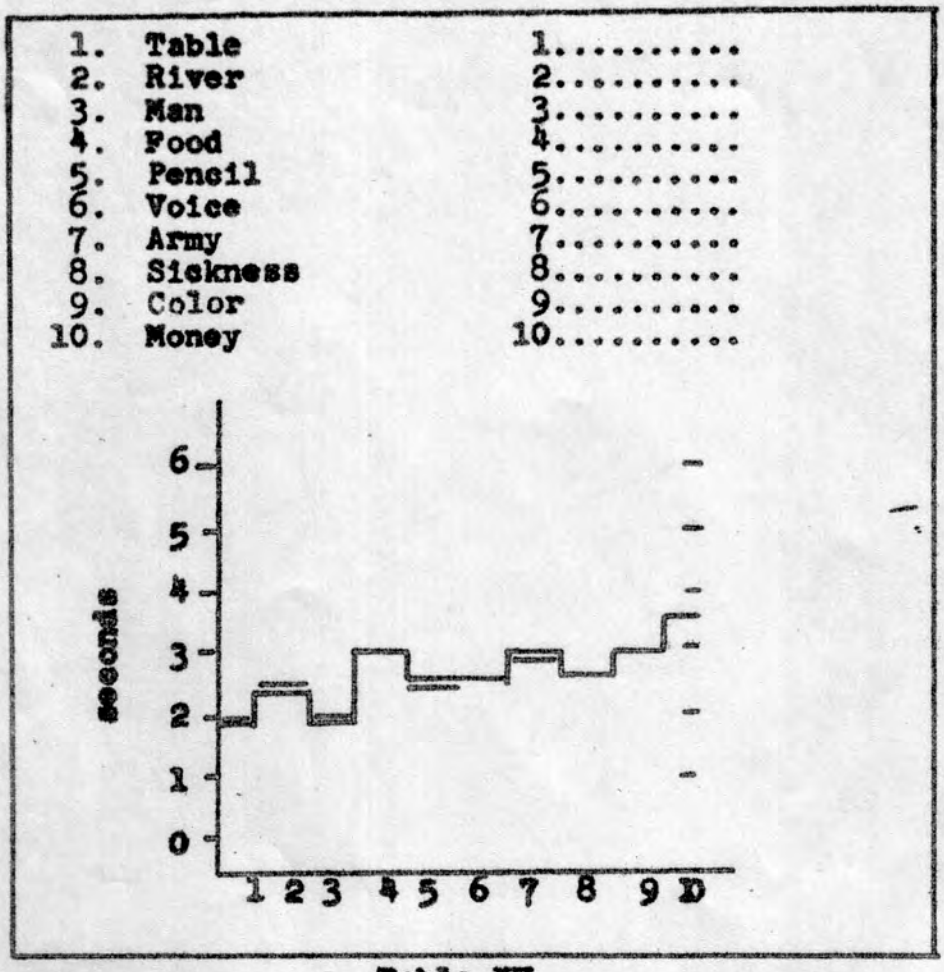


Table XV.

Association times below the single-line cut-off fall within the 80 percentile of the normal, below the double-line within the 90 percentile.

Man	(Woman)
Cabbage	(Vegetable)
Hard	(Soft)
Eagle	(Bird)
Ocean	(Sea)
Lamp	(Light)
Long	(Short)
Tobacco	(Smoke)
Scissors	(Cut)
Blossom	(Flower)

Table XVI

80% of normal controls give at least four of the "common" responses (in brackets) taken from the Kent-Rosanoff list.

SENSATION: hyperesthesia	hypoesthesia	anesthesia	paresthesia
PERCEPTION: illusions	pseudo hallucinations	hallucinations	body image disturbances
ASSOCIATION: homophonic	increased association time	decreased association time	
THINKING: blocking	decreased stream	increased stream	
concrete	symbolical	perseverative	obsessive
overvalued ideas	non systematized delusions	systematized delusions	megalo or micromanic delusions
persecutory delusions	autistic	dissociated	confused
JUDGEMENT: impaired personal	impaired non-personal		
INSIGHT:		partial	absent
EMOTIONAL: richness or poverty	ambivalence	incontinence	inappropriateness
suspiciousness	fear	anxiety	phobias
SENSITIVITY: loss of moral feelings	loss of esthetic feelings	loss of vital feelings	
MOOD: euphoric	apathetic	dysphoric	
AFFECT: fatigue	tension	aggressiveness	pathological impulse
INSTINCT: refusal of food	decreased food or fluid intake	increased food or fluid intake	specific deviation of appetite
impotency	increased libido	homosexuality	other sex deviations
self mutilation	suicidal tendencies		
MOTOR ACITIVITY: hypoactivity	hyperactivity	agitation	motor incoherence
amimia	hypomimia	hypermimia	gesticulation and grimacing
autistic excitement	stupor	negativism	flexibilitas cerea
stereotypy	mannerisms	loss of automatic coordination	loss of spontaneous activity
SPEECH: decreased speech	increased speech	logorrhea	incoherence
mutism	echolalia	alliteration	verbigeration
aphasia	paraphasia	neologism	confabulation
CONSCIOUSNESS: clouded	somnolence	sopor	coma
delirium	twilight	oneiroid	
ORIENTATION: completely disoriented	disoriented to time	disoriented to place	disoriented to person

ATTENTION:			
VIGILANCE: hypervigil	hypovigil		
TENACITY: hypertenax	hypotenax		
CONCENTRATION:		poor	absent
PERSONALITY: depersonali-sation	ego split		
INTELLIGENCE:	above average		below average
MEMORY: hypermnesia	paramnesia	amnesic syndrome	
total amnesia	partial amnesia	retrograd or anter-ograd amnesia	
impairmed memory for immediate past	for recent past	for remote past	
SLEEP: hypersomnia	hyposomnia	insomnia	somnus vigilans
somnoloquism	somnambulism	nightmares	enuresis
OTHERS:			

Table XVII

During the trial period 30 to 90 mgs. of Sordinol were administered daily in three equally divided doses.

Based on the daily notes and check lists the drug's principal effects were seen in the following areas: integration of mental activity, affectivity, arousal, behavior and social contact. In 9 patients improvement was manifested in mental integration as a reduction of disorders of thought and perception together with positive behavioral changes. There was better social contact. On the other hand, the activity (arousal parameter) of 3 patients decreased and 4 became depressed (affectivity parameter). Simultaneously a general improvement was noted in Word Association Time while the Conformity Index did not show any conclusive changes.

The following side effects occurred: paroxysmal tachycardia (1), dry mouth, skin and scalp (3), facial flushing (4), extrapyramidal symptoms (10), depressive mood change (4), transient drowsiness (14). Medication had to be discontinued in 1 case because of side effects (paroxysmal tachycardia). The majority of the extrapyramidal symptoms occurred in the 3rd week and were controlled with anti-Parkinsonian medication. Drowsiness was prominent at the beginning of the trial but diminished during the course of treatment, while dryness of skin and scalp increased as time passed.

Of the 20 cases, 9 showed clinical improvement (3 marked and 6 moderately), one became less controlled, 4 became more depressed and another 6 remained unchanged. Global impressions collected from the ward staff were in agreement with these findings.

The observation that this drug was therapeutically effective in certain chronic schizophrenic patients where previous treatments had failed suggests that Sordinol may deserve a place among the clinically used antipsychotic compounds.

Opinion: Therapeutic in chronic schizophrenics.

(Ban, T.A., Ferguson, K. Lehmann, H.E. The Effect of Clopenthixol on Chronic Psychiatric Patients.
American Journal of Psychiatry, 119:984-985, April 1963)

III. EARLY DRUG EVALUATION IN ACUTE PSYCHIATRIC PATIENTS.

III. (1) Early Drug Evaluation with CI-383 in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the drug.)

A clinical trial was carried out with CI-383 over a 10-week period with 16 newly-admitted schizophrenic patients.

The following baseline tests were conducted biweekly: laboratory (Table VIII); physical (Table IX); and the Verdun Target Symptom Rating Scale (Table XI) completed at weekly intervals.

Medication was administered in 100 to 300 mgs. dosage daily, divided in four doses.

In 5 of the 16 cases medication had to be discontinued during this period due to insufficient clinical improvement (2 were discontinued in the 5th week, 1 in the 6th, 1 in the 7th and 1 in the 8th week); in 4 cases medication was discontinued because of side effects, namely, repeated palpitations and tachycardia that started approximately 20 to 60 minutes after the drug was given and subsided spontaneously within 2 hours.

On the basis of findings on the Verdun Target Symptom Rating Scale the compound appeared to be most effective in controlling excitement and hallucinations and counteracting hostility. It is also effective but somewhat slower in ameliorating suspiciousness and anxiety. Its effect on disturbance of thinking increases with the increase in dosage and length of administration. In regard to depression, there was some amelioration of mood in patients with depressive features but it should be noted that depressive mood changes occurred also in a patient as a side effect (1 patient). A slight reduction in weight was noticed in patients after 4 weeks, this trend being maintained throughout the trial.

Opinion: Therapeutic in newly admitted schizophrenics; toxicity (cardiac) needs to be confirmed.

III. (2) Early Drug Evaluation with G-35020 in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antidepressant properties of the compound.)

A clinical trial was carried out with G-35020, over a period of 10 weeks, with 25 newly admitted patients who presented a depressive syndrome as the principal or at least as a prominent clinical feature.

The following tests were conducted: laboratory; physical;. In addition the Verdun Depression Rating Scale was completed at daily intervals in the first week, three times in the second, two times in the third and weekly thereafter.

Treatment usually began at 75 mgs. daily in 3 equally divided doses. This was increased to 150 mgs. and if required to 225 mgs. Patients were kept on the least effective dosage until the end of the 10-week clinical trial. There were only 2 cases in whom medication had to be discontinued because of side effects.

Results were evaluated in percentage changes of the individual patient's score. The total score obtained before commencement of therapy was taken as a baseline. A 75 to 100% reduction of the score was classified as an 'excellent' result, a 50 to 75% reduction as 'good' and a 25 to 50% reduction as a 'fair' result of the therapy. Below a 25% reduction of the score, patients were considered as 'failures'. It was found that the evaluation by rating scale corresponded very closely with the clinical impression collected from the ward staff after termination of the trial.

The results obtained according to the rating scales and their distribution among the diagnostic categories are shown in Table XVIII.

	Excellent	Good	Fair	Failure
Manic-depressive	8	2	1	2
Involutional melancholia	3	2	1	1
Schizophrenia	1	1	1	1
Neurotic depressive reaction	1	0	0	0
Total	13	5	3	4

Table XVIII

A variety of side effects was encountered in about one-third of the patients. Insomnia was seen in four, hypomania occurred in 2 cases and dryness of mouth, sweating and mydriasis in 1 case each. 1 patient developed definite extrapyramidal symptoms. Our findings also revealed that it required 2 to 3 days for a response to show on the rating scale; that the peak effect was observed between the 2nd and 3rd week and that older and agitated patients required longer periods to respond than others; that within an 8-week period 75% of the patients treated with the drug recovered or were much improved. (Additional information: in a single dose (50 mgs.) psychophysical study, the drug evoked a slight reduction of psychomotor functioning.)

Opinion: Therapeutic in newly admitted depressed patients.

(Ban, T.A. and Lehmann, H.E. Clinical Trial with Desmethylimipramine (G-35020), A New Antidepressive Compound. C.M.A.J. 86:1031-1032, June 2, 1962.)

III. (3) Early Drug Evaluation with Largactil in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the compound).

A clinical trial was carried out with Largactil over a period of 6 weeks with 10 newly admitted schizophrenic patients.

The following tests were conducted: laboratory; physical. The patients were interviewed and assessed on three rating scales (Verdun Target Symptom, Depression and Sociability (Table XIX) Rating Scales).

	1	2	3	4	5	6	7	8
1. Interest in television or radio								
2. Interest in reading								
3. Participation in conversation								
4. Socialisation								
5. Social adaptation (at work or other)								

Table XIX.
(0-1-2-3)

Immediately after arrival and before receiving medication a short battery of psychophysical tests selected from the Verdun Psychophysical Battery (Table XX) (Reaction Time, Tapping Speed, Cancellation Time and Stroop Test) were administered.

1. Tapping Speed
2. Reaction Time
3. Stroop Test
4. Critical Flicker Fusion Frequency
5. Spiral After-Image
6. Trecktracer Time and Error
7. Time Production
8. Time Reproduction
9. Body Sway
10. After-Image Disappearance
11. Wechsler Memory Scale: Storytelling
12. Digits Forward and Backward
13. Paired Associates Learning
14. Word Association Test
15. Cancellation Test

Table XX

The physical measurements and ratings were done weekly during the 6-week trial period and laboratory and psychophysical tests were repeated after 3 weeks and again after 6 weeks.

In all cases Largactil was used freely in the dosage from 900 to 4000 mgs. daily.

The results of the weekly psychiatric ratings are shown in Figures IV and V. Figure IV presents the weekly mean ratings for each of the three rating scales employed.

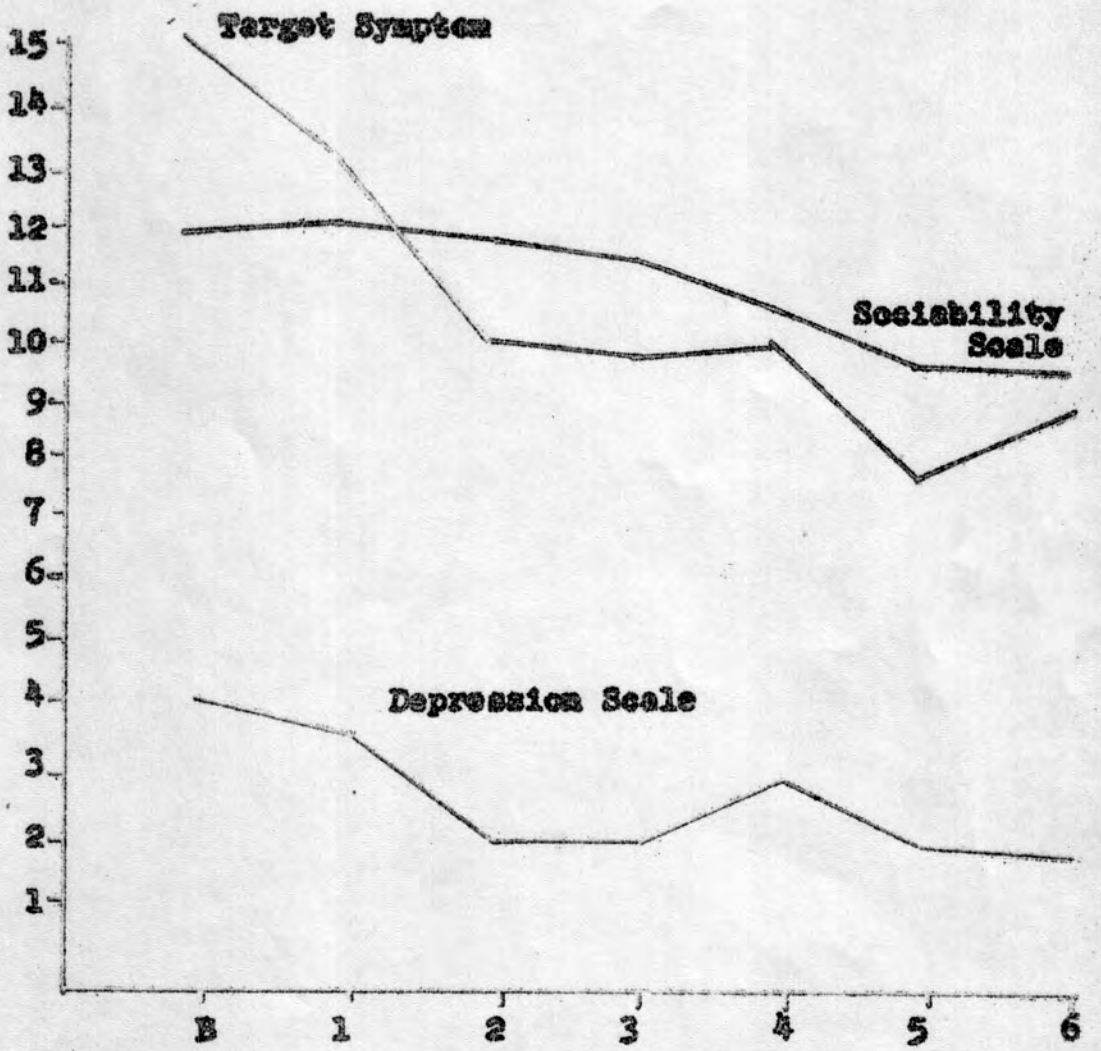


FIGURE IV.

Figure V presents the significance of these weekly changes (Wilcoxon and Sign tests).

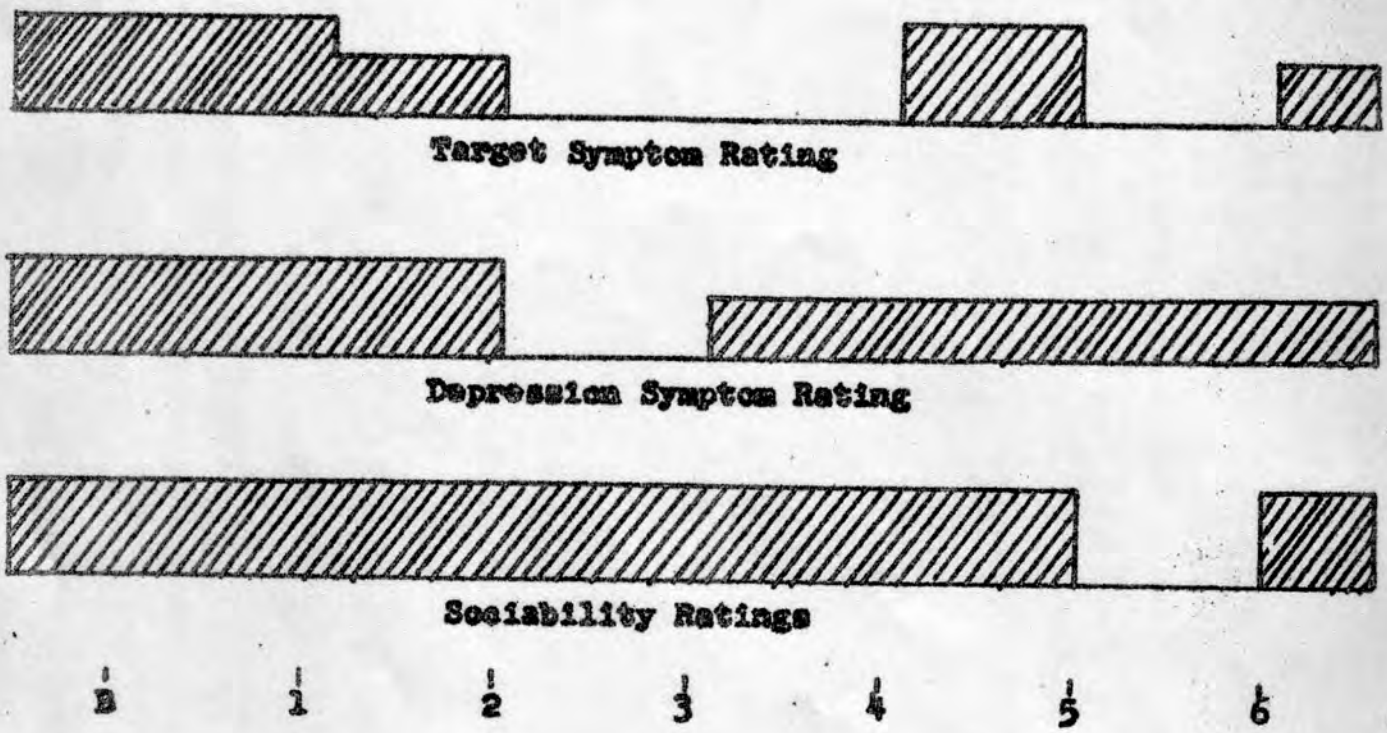


FIGURE V.

From Figure V it can be seen that all symptomatology was lowered during the six-week trial period. There was a significant drop ($p \geq .05$) in the score of the Target Symptom Rating Scale after the 1st week and this remained at a decreased level for the remainder of the trial with exception of the 5th week during which 3 patients had a brief relapse. Depression symptoms became significantly lowered ($p \geq .01$) by the second week and remained at the lower level ($p \geq .05$) until the end of the trial. In the 4th week 2 patients became considerably more depressed than they had been for most of the trial however 1 recovered completely and the other showed some improvement before the end of the trial. Sociability ratings showed few changes, but 6 patients showed some gradual improvement in this area so that the over-all drop became statistically significant ($p \geq .01$) in the 5th week.

Our findings further indicated that at the end of 2 weeks the symptom areas which had decreased the most were anxiety, depression, object relations, and expected social response; whereas those which had dropped the least were memory disturbance, hallucinations, thought disorder and delusions.

At the end of the 6-week period the most ameliorated symptoms were anxiety, object relations, suspiciousness, expected social response and excitement. The least were hallucinations, delusions, memory disturbance and impairment of consciousness.

7 of the 10 patients refused psychophysical testing in the pre-trial period; however all patients were cooperative after the 3rd and most after the 6th week. Because of these gaps in the pre-trial testing most of the statements that follow are based on a comparison of the 2nd and 3rd testings. From a population of 9 patients who were tested at least twice, the following trends were noted: the only consistent findings were a drop in reaction time which occurred in 7 of the 9 patients. Both of those whose reaction time slowed manifested a corresponding increase in total target symptomatology. Neither the Tracktracer, the Cancellation Test, nor the Stroop Test showed any consistent pattern, but it should be noted that 2 patients who did not improve clinically manifested this also in lengthened Cancellation and Tracktracer Times as well as in slower Reaction Time.

Drowsiness was the commonest side effect and occurred in 8 patients at some time during the trial. Vertigo was the next most frequent and occurred in 7 patients. Constipation was reported in 5 patients, headache in 4, dry mouth in 3, coated tongue in 3, tremors in 2, and unsteady gait in 2. In 1 case only there occurred itching of the skin, cerebral seizures, fainting attacks, nausea, vomiting, abdominal cramps, rigidity, insomnia and blurred vision. In no cases were the side effects or laboratory findings sufficiently severe to cause the drug to be withdrawn.

The first changed induced by Largactil came in the area of affect (anxiety and depression), followed by changes in the arousal parameter (excitement). During this 6-week study period symptoms denoting mental integration (delusions, hallucinations, thought disorder) showed little change.

Opinion: Therapeutic in newly admitted schizophrenics. (Symptoms of perceptual and thought disorder improve long after symptoms of excitement and affect have improved.)

III. (4) Early Drug Evaluation with Majeptil in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested psychotropic properties of the compound.)

Majeptil was administered to 5 newly admitted manic-depressive, manic patients for a period of 3 weeks.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory; physical; the Verdun Side Effect Check List and Target Symptom Rating Scale completed at regular intervals.

Majeptil was administered with a dosage schedule of 30 mgs. daily, in three divided doses. This dosage was maintained for a few days (3 to 5 days) until a hyperkinetic-hypertonic syndrome became prominent. Then the medication was withdrawn until the disappearance of marked extrapyramidal manifestations. 'Chemoshock' was repeated three times.

4 of the 5 patients showed excellent and 1 good results to Majeptil therapy. There was no failure in our small group. This prominent action of the drug in this diagnostic category suggests a special role for this compound in the treatment of manic patients.

Opinion: Therapeutic in newly admitted manics.

(Ban, T.A., Papathomopoulos, E. and Schwarz, L. Clinical Studies with Thioproperazine (Majeptil). Journal of Comprehensive Psychiatry, 3:284-291, October 1962.)

III. (5) Early Drug Evaluation with R-1625 in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the compound.)

A clinical trial was carried out over a 6-week period with 10 newly admitted schizophrenic patients.

Evaluation was based on a battery of tests and examinations: laboratory; physical. The patients were interviewed and assessed on three rating scales (The Verdun Target Symptom, Depression and Sociability Rating Scales). Immediately after arrival and before receiving medication they were administered a short battery of psychophysical tests selected from the Verdun Psychophysical Battery (Reaction Time, Tapping Speed, Cancellation Time and Stroop Test).

The physical measurements and ratings were done weekly during the 6-week trial period and laboratory and psychophysical tests were repeated after 3 and again after 6 weeks.

In all cases R-1625 was used freely in the dosage from 10 to 100 mgs. daily.

2 of the 10 patients were taken off R-1625 during the trial period, the first after 1 week because of side effects on taking 12 mgs. daily (nausea, vomiting, tremor) and the other was discharged from the hospital at the end of the fourth week at which time her score on all three scales was '0'. The global impression of the ward staff was that she had improved greatly.

On Figure VI the weekly significant changes (Sign test) of the three rating scales are presented.

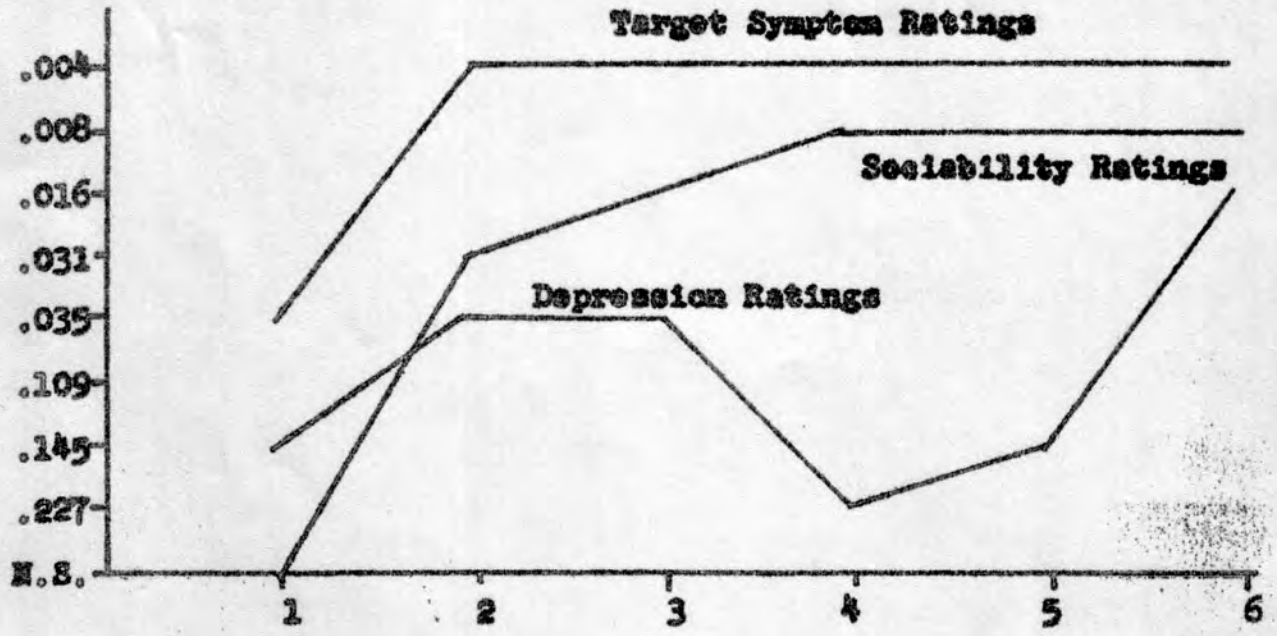


FIGURE VI.

This shows that on the Target Symptom Rating Scale there was significant improvement at the end of the 1st week ($p = .035$) becoming more expanded at the end of the 2nd week ($p = .004$) and continuing on this level of probability until the end of the trial. On the Depression Rating Scale there was significant improvement at the end of the second week ($p = .035$) and this became more marked in the 6th week ($p = .016$). On the Sociability Rating Scale there were significant changes at the end of the second week ($p = .031$) which became more pronounced at the end of the 4th week ($p = .008$) and remained so until the end of the trial.

The individual target symptom which showed the most marked changes at the end of the 2nd week was excitement ($p = .031$); at the end of the 6th week there was significant change in the following areas: hostility ($p = .008$), object relations ($p = .016$), social response, suspiciousness, anxiety, all at the $p = .031$ level of confidence. Among the psychophysical tests only the reaction time was significantly decreased in 6 patients at the end of the 6-week period. Other changes were inconsistent.

At the end of the trial all of the 8 patients were considered to have improved slightly, 4 moderately and 4 markedly.

The most common side effect was drowsiness which occurred in 6 patients. This was followed by constipation in 5 and tremors in 4. Nausea occurred in 2 and vomiting in 1 case and was sufficiently severe to cause the drug to be withdrawn. Other side effects included: dry mouth (3), stuffy nose (2), unsteady gait (2), and excessive salivation (2).

The order of changes induced by R-1625 was as follows: the first changes came in the area of arousal, followed by changes in the affective (anxiety and depression) parameter. During this 6-week study period symptoms referring to mental integration (delusions, hallucinations, thought disorder) showed little alteration.

Opinion: Therapeutic in newly admitted schizophrenics.

III. (6) Early Drug Evaluation with Surmontil in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antidepressant effect of the compound.)

A clinical trial was carried out with Surmontil over an 8-week period with 20 newly-admitted depressed patients (manic-depressive, depressed 6; involutional melancholia 3; schizoaffective psychosis 3; neurotic depressive reaction 8).

Evaluation was based on a battery of tests and examinations: laboratory; physical; the Verdun Target Symptom and Depression Rating Scales, completed at regular intervals.

Medication was given in the dosage of 150 to 300 mgs. daily in three divided doses.

Of the 20 patients 8 did not complete the full trial period. 2 patients were discharged at an early date, 1 with good improvement and 1 against advice. Drug administration in 3 cases was discontinued because of insufficient effect after 3 weeks, and in 2 cases because of adverse effect, in 1 patient because of toxic confusional state and in another because of hypote

Findings on the two rating scales were tested for signifance with two non-parametric tests (the Sign and Wilcoxon tests). on the Verdun Target Sym tom Rating Scale changes in the total symptomatology of the population were significant at the .01 level of confidence from the 1st week after medication until the end of the drug trial. Although the drug was effective within a week the gross quantitative drop in symptomatology took place between the 2nd and 4th week of drug administration. Five specific target symptoms showed improvement during the trial: depression and thought disturbance were reduced from the 2nd week (both at the .01 level of confidence), anxiety and suspiciousness from the 3rd week (the first at the .01 and the second at the .02 level of confidence). Excitement was reduced

from the 4th week (.05 level of confidence). On the Verdun Depression Rating Scale changes in the total symptomatology were significant, (at the .01 level of confidence) a week after medication until the end of the trial. The specific depression scale items showed improvement as follows: mood, facial expression, retardation improved significantly from the first week (the first 2 on the .01 and the third at the .02 level of confidence). Depressive ideation was reduced and sleep improved from the 2nd week (both at the .01 level of confidence). 9 patients gained weight (mean gain 9 pounds during the trial period). The most frequent side effect was tremor (5), dry mouth (4), blurred vision (4), drowsiness (3), palpitations (3) and headache (3). All other clinical side effects occurred in 1 patient: toxic confusional state, hypotension, skin rash, dizziness, tension.

Further analysis of our findings indicated that the drug is most effective in the treatment of involutional depressions, somewhat less effective in manic depressive and reactive depressions and least effective in schizoaffective depressions.

Opinion: Therapeutic in newly admitted depressed patients.

III. (7) Early Drug Evaluation with Tarasan in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the compound.)

A clinical trial was carried out with Tarasan over a 6-week period with 10 newly admitted schizophrenic patients.

Evaluation was based on a battery of tests and examinations: laboratory; physical. The patients were interviewed and assessed on three rating scales (the Verdun Target Symptom, Depression and Sociability Rating Scales).

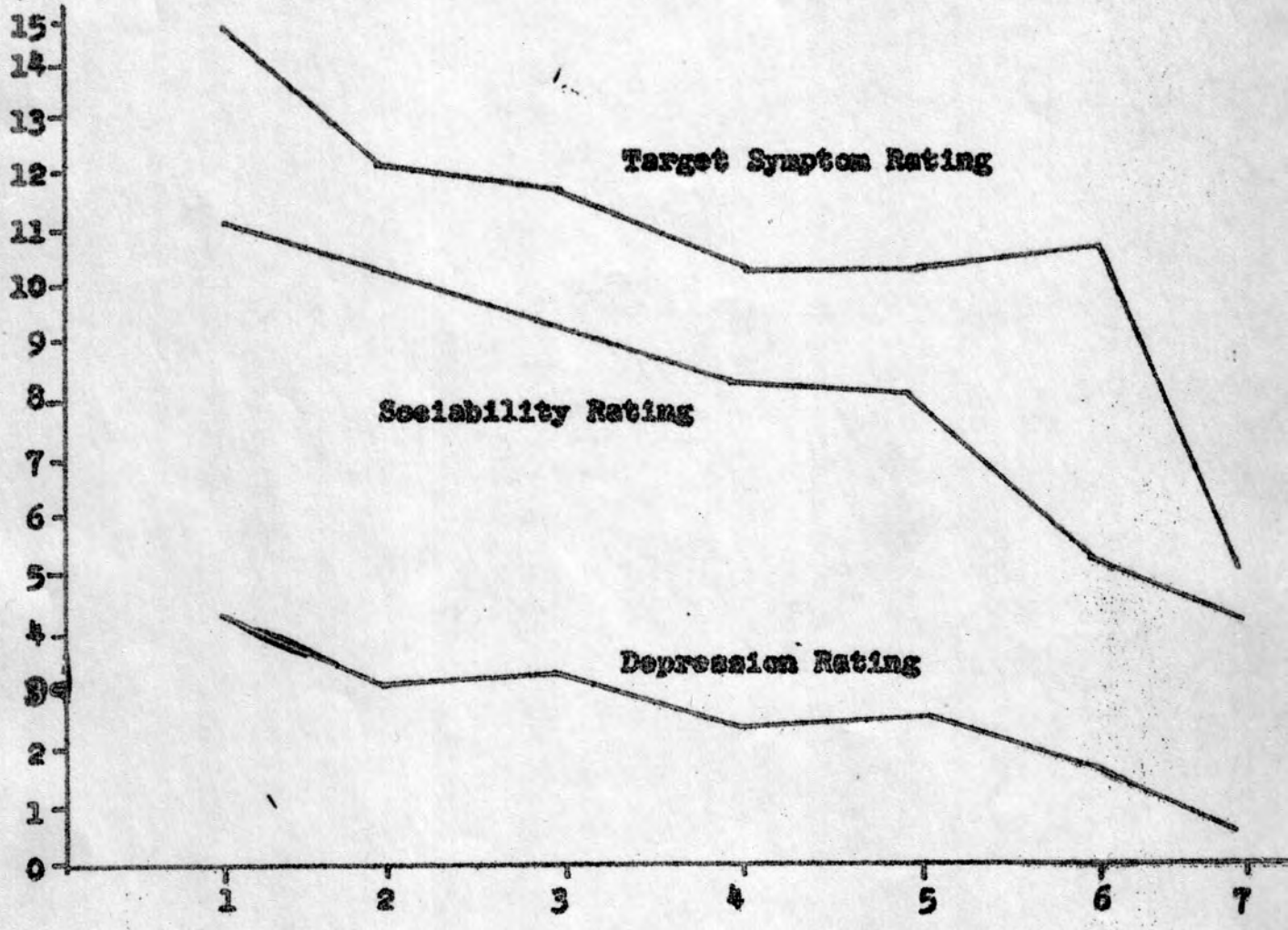
Immediately after arrival and before receiving medication a short battery of psychophysical tests selected from the Verdun Psychophysical Battery (Reaction Time, Tapping Speed, Cancellation Time and Stroop Test) were administered.

The physical measurements and ratings were done weekly during the 6-week trial period and laboratory and psychophysical tests were repeated after 3 weeks and again after 6 weeks.

In all cases Tarasan was used in the dosage range from 50 to 1000 mgs. daily.

Of the 10 patients 4 had to be taken off medication because of uncontrollable behavior in this dosage range; one of them after the 1st week, one after the 3rd and two after the 5th week of medication.

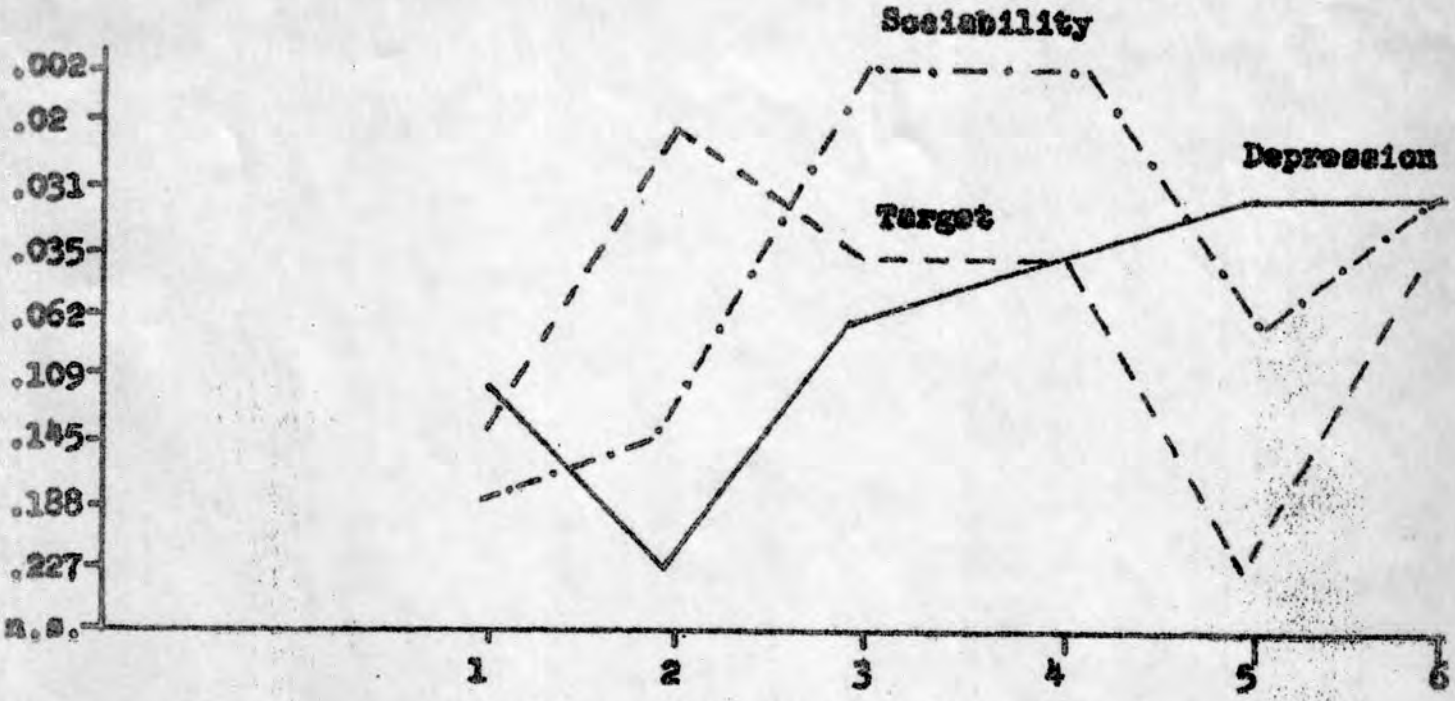
The weekly mean scores for symptomatology on the three rating scales all show a gradual decline (Figure VII) over the 6-week period. Only in the 5th week on the Target Symptom Rating Scale is there some interruption of this downward trend.



Weekly Mean Ratings.

FIGURE VII.

The statistical significance (Sign test) of these changes is shown in Figure VIII.



Significance of Changes in Weekly Ratings.

FIGURE VIII.

On the Target Symptom Rating Scale there is a significant improvement ($p \geq .02$) at the end of the second week. There is some reduction in the level of significance ($p = .035$) with a marked drop in the 5th week ($p = .227$). By the 6th week the previous level had been restored ($p = .031$). On the Depression Rating Scale there was a gradual increase of significance from the 2nd week ($p = .227$) to the 6th week ($p = .031$). On the Sociability Rating Scale the first significant changes took place in the 3rd week ($p = .02$).

The individual target symptoms which show the most striking improvement are in the 3rd week: excitement ($p = .08$), suspiciousness ($p = .016$), in the 6th week depression ($p = .031$), delusions ($p = .188$), suspiciousness ($p = .344$), anxiety ($p = .344$), improvement in object relations ($p = .344$).

Among the psychophysical tests the mean results of the Cancellation test (time and error both) show a significant decrease.

The commonest side effects were vertigo and drowsiness which were reported by 6 patients, dry mouth, constipation, insomnia and nausea reported by 5. 4 patients had coated tongue, 3 stuffy nose, another headache and 3 anorexia. Other side effects included fainting, tremors, skin rash in 2. 1 patient had blurred vision and watering eyes and another a grand male seizure.

The order of changes induced by Taraxan is as follows: the first changes came in the area of arousal followed by changes in the area of affectivity (anxiety and depression). Towards the end of the study changes began in the area of mental integration.

Opinion: Therapeutic in newly admitted schizophrenics.

III. (8) Early Drug Evaluation with Valium in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested possible tranquillizing properties of this drug.)

A clinical trial was carried out with Valium over an 8-week period with 15 newly admitted schizophrenic patients.

Evaluation was based on a battery of tests and examinations: laboratory; physical; the Verdun Target Symptom Rating Scale; completed at regular intervals.

Valium was administered in a dosage range of 30 to 90 mgs. daily in three divided doses.

The trial was originally designed for 8 weeks but 10 of the patients had to be taken off the drug within 3 weeks and 1 in the 4th week of the trial because of inadequate control of undesirable behavior and absence of any therapeutic effect on the psychotic manifestations.

Analysis of our findings indicated that the drug did have some beneficial effect in reducing anxiety.

Opinion: Ineffective in newly admitted schizophrenics.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit II. Canadian Psychiatric Association Journal. In Press.)

IV. COMPARATIVE STUDIES ON THE RELATIVE EFFECTIVENESS OF COMPOUNDS.

IV. (1) The Comparative Effectiveness of Tofranil, G-35020 and Ensidon

30 chronic hospitalized psychotic patients with depressive mood change or apathy, equally subdivided into three groups, were administered Tofranil, G-35020 and Ensidon for a period of 12 weeks.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory (Table VIII); physical (Table IX); the Verdun Target Symptom (Table XI) and Depression Rating Scales (Table XII) and the Verdun Side Effect Check List (Table X).

Administration of medication during the experimental trial was single blind and followed an increasing dosage schedule (100 to 200 mgs. daily in 4 divided doses).

No toxic effect in the laboratory tests was revealed. On the physical tests, blood pressure dropped significantly in the G-35020 group ($p > .001$, Sign test); while in the Ensidon group it started to rise but not frequently enough to reach significance. The Tofranil group showed no pattern of change. On the other hand, pulse rates rose significantly in the Tofranil group ($p > .01$) and fell in the Ensidon group ($p > .01$) while the G-35020 group did not show any pattern of change.

Results of the psychiatric ratings indicated certain clinical trends, but were not consistent enough to reach statistical significance. Total Target Symptom ratings indicated slight general improvement in the condition of 7 of the 10 Tofranil subjects. In the G-35020 group no trend was evident, but 5 patients improved, 4 became worse and 1 remained unchanged. The Ensidon group showed approximately the same proportion of changes as the G-35020 group: 5 patients improved, 3 became worse and 2 remained the same.

In the Tofranil group, 6 patients showed a decrease in depressive symptoms from the 6th week on the trial period and in the G-35020 group, the same improvement was noted from the 10th to the 12th weeks of the trial. The Ensidon group again showed no consistent trend. Tension and irritability however showed an increase in 40% of the patients in each group.

On the basis of our study with the three experimental compounds Tofranil appeared to have the strongest psychotropic (anti-depressive and antipsychotic) effect, although these effects were relatively slight. G-35020 showed a slight antidepressant effect late in the trial and Ensidon had no notable effect on psychiatric symptoms.

Opinion: Order of antidepressant potency: Tofranil, G-35020, Ensidon.

IV. (2) The Comparative Effectiveness of R-1625 and Permitil.

A comparative 6-week clinical trial was conducted on 30 female psychotic patients with R-1625 and Permitil. Patients for this study were selected on the basis of the chronicity of their illness and inadequate response to previous therapies. They were subdivided into 2 groups, matched as to age and length of hospitalization.

The following tests were conducted: laboratory; physical. Their psychopathology was assessed by rating scales containing items under the headings of emotion, perception, thought process, thought content, motivation, sleep, appetite.

One group was placed on R-1625 and the other on Permitil medication in dosages increasing within 4 weeks from 3 x 1 to 3 x 4 mgs. and 3 x .5 to 3 x 2.0 mgs. respectively.

Both medications appeared to improve symptoms related to the parameter of mental integration. R-1625 appeared to be superior in counteracting perceptive disorders. It should be noted however that both compounds produced therapeutic effects in both areas. The sleep disturbances of 5 patients improved while they were on R-1625, while the activity (motivation) of 3 patients improved while on Permitil. Our trial suggested that R-1625 may be preferable where hyperactivity and agitation are associated with pathology of perception and insomnia, while Permitil may be preferable where apathy and withdrawal are associated with thought disorder (Table XXI).

Improvement was shown in:	Haloperidol	Permitil
Emotion	1	3
Perception	7	3
Thought Process	5	10
Thought Content	7	5
Motivation	0	3
Sleep	5	0
Appetite	2	0

Table XXI

This study revealed no organ toxicity with either of these compounds. The principal clinical side effects were drowsiness with R-1625 (4), insomnia with Permitil (3), extrapyramidal symptoms with both (9).

Opinion: Equally antipsychotic but areas of maximal effectiveness different.

(Ban, T.A., Stonehill, E. and Lehmann, H.E. Butyrophenones in Psychiatry.
Symposium, L'Annemeistion, Quebec, January 10, 1964.
In Press.)

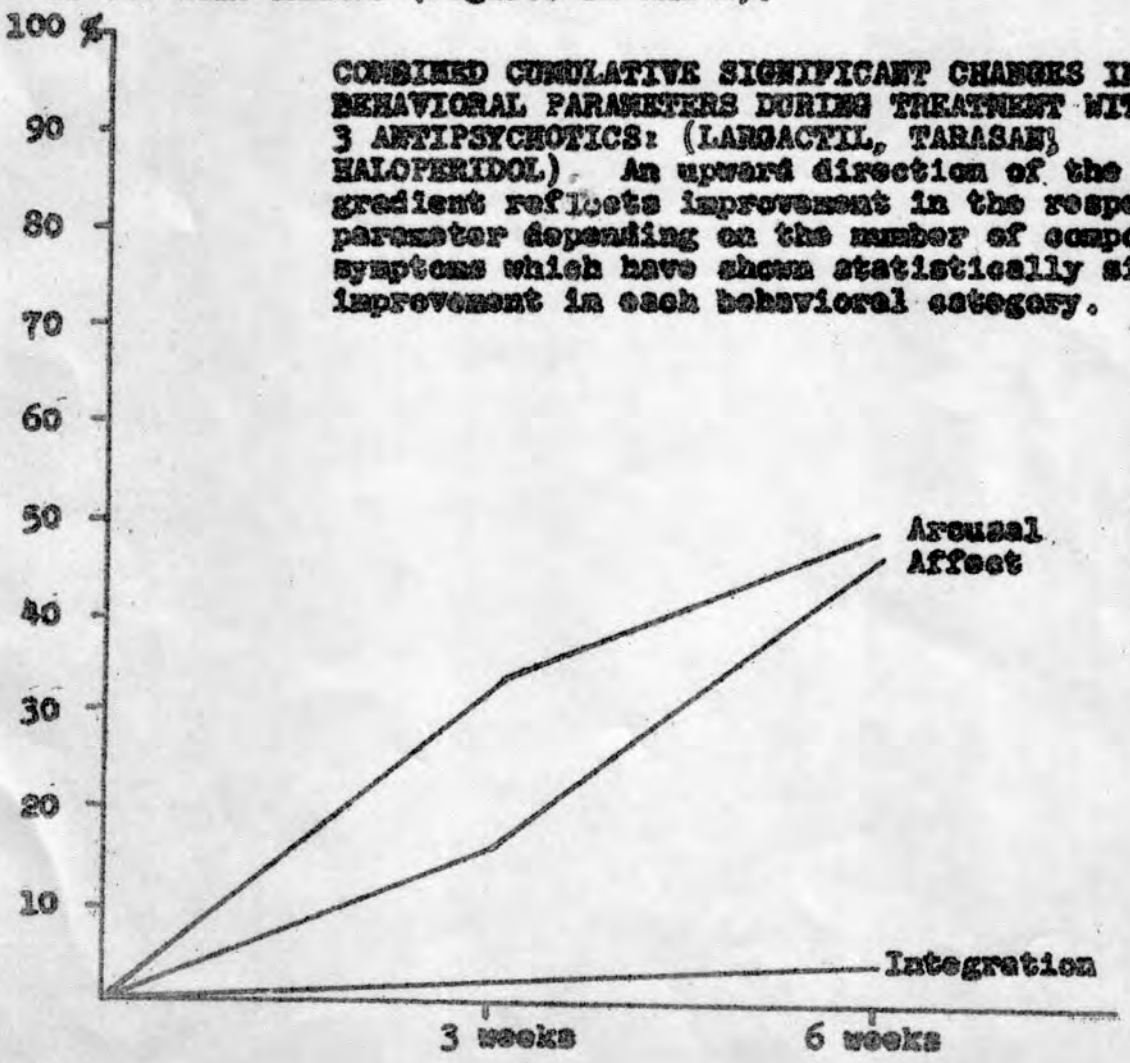
IV. (3) The Comparative Effectiveness of R-1625, Largactil and Tarasan.

30 newly admitted schizophrenic patients equally divided into 3 categories were administered R-1625, Largactil and Tarasan for a period of 6 weeks.

The following tests were conducted: laboratory; physical. The patients were closely followed by clinicians for day-to-day manifestations of their psychotic condition, and at weekly intervals their behavior and mental status were recorded on the Verdun Target Symptom, Depression and Sociability Rating Scales. The behavioral manifestations recorded were brought together under 3 categories which designate 3 parameters of mental functioning. The 3 parameters on which we oriented our observations were: 1. arousal, 2. affect and 3. integration.

The three drugs used were R-1625 representing the butyrophenones, Largactil representing the phenothiazines, and Tarasan representing the thioxanthenes. They were administered in the following dosages: R-1625, 10 to 100 mgs., Largactil 900 to 4000 mgs. and Tarasan 50 to 1000 mgs., daily.

Each group of patients receiving an antipsychotic drug reacted in the same manner (Figures IX and X).



COMBINED CUMULATIVE SIGNIFICANT CHANGES IN BEHAVIORAL PARAMETERS DURING TREATMENT WITH 3 ANTIPSYCHOTICS: (LARGACTIL, TARASAN, HALOPERIDOL). An upward direction of the gradient reflects improvement in the respective parameter depending on the number of component symptoms which have shown statistically significant improvement in each behavioral category.

FIGURE IX.

INDIVIDUAL CUMULATIVE SIGNIFICANT CHANGES IN BEHAVIORAL PARAMETERS DURING TREATMENT WITH 3 DIFFERENT ANTIPSYCHOTICS.

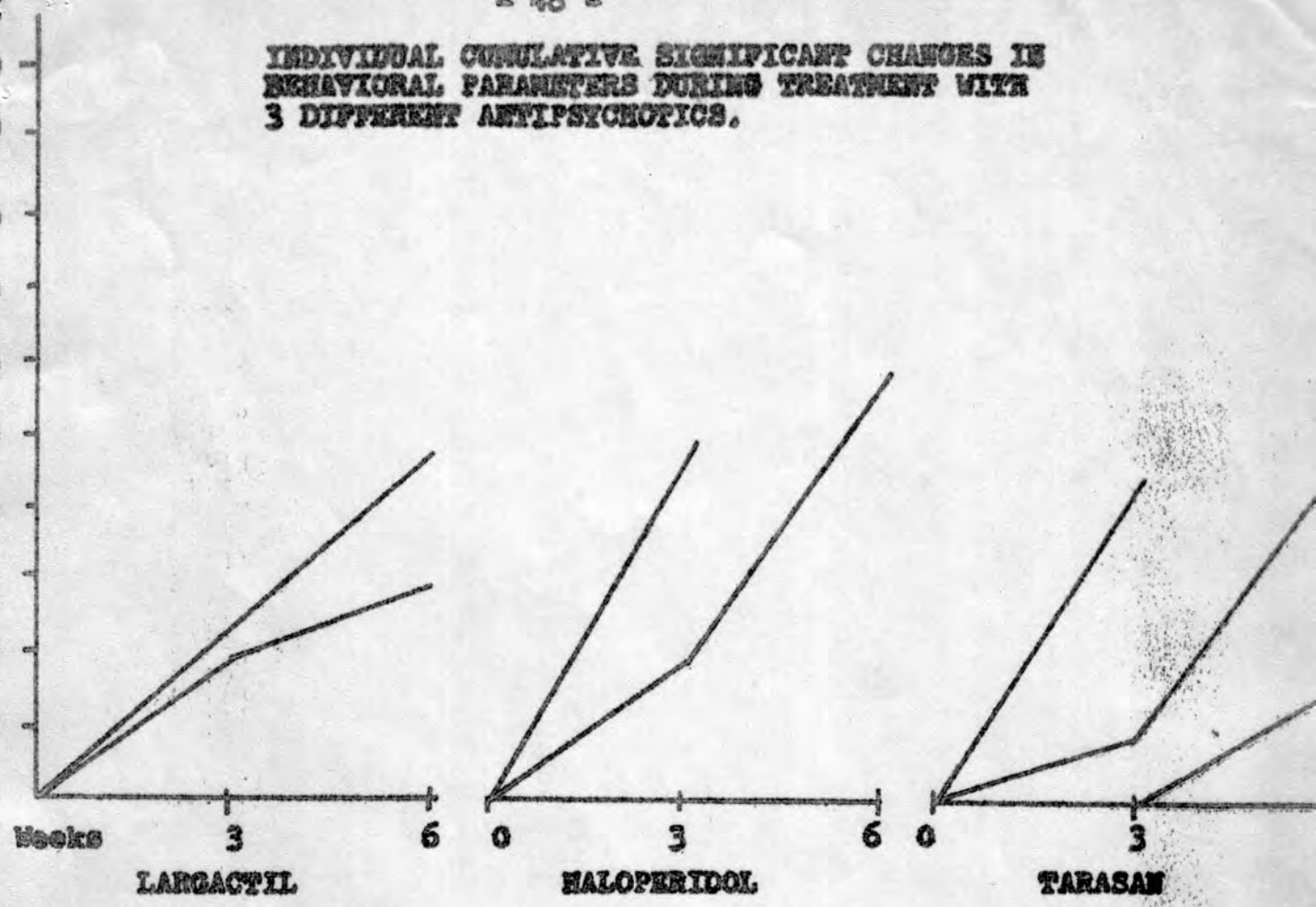


FIGURE X.

There was a rapid improvement of symptoms on the arousal parameter as excitement and agitation subsided soon after pharmacotherapy commenced. This was followed by a less rapid but still dramatic improvement in the sphere of affect which became evident in a lessening of anxiety, tension and depression and in greater accessibility of the patients. However the most specific psychotic symptoms such as hallucinations, delusions and thought disorder were hardly affected at all in the first 6 weeks of treatment with the 3 antipsychotic compounds. There were among the 30 patients of our sample some in whom such fundamental improvement did occur, but in the close follow-up studies of the whole sample on a quantitative basis, the changes observed on the integration parameter were not large enough to become statistically significant.

The pattern of improvement over this time showed a very similar distribution of the therapeutic effects in each of our 3 groups of schizophrenic patients, suggesting a similar mode of action for each of the three chemically different major tranquillizers.

A slight effect on the integration parameter, due to improvement in the symptom of delusions, appeared only in the group treated with Taractan, but the number of patients was very small. Hence the over-all similarity of sequential symptom reduction is probably more significant than the one slight difference since this might well have been due to sampling. It should also be noted that the group receiving Largactil, and exhibiting the least improvement, was composed of patients with higher pre-treatment morbidity ratings than the other two groups, since patients were assigned to the different drugs as they were admitted to the hospital and were not matched for degree of initial pathology.

Opinion: Equally effective. Order of effect: arousal, affectivity, mental integration.

(Ban, T.A., Stonehill, E. and Lehmann, H.E. Butyrophenones in Psychiatry. Symposium, L'Annonciation, Quebec. Jan. 10/64. In Press.)

IV. (4) The Comparative Effectiveness of R-1625, McN-JR-2498 and McN-JR-3345 in Chronic Psychiatric Patients.

The experimental compounds were administered in succession for 8-week periods each to 15 chronic schizophrenic patients, following a Latin square design.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory; physical; the Verdun Side Effect Check List and the Verdun Target Symptom Rating Scale.

The drugs were administered in increasing dosages from 1.5 to 30 mgs. in 3 divided doses for the R-1625 and McN-JR-2498 groups, and from 60 mgs. to 600 mgs. for the McN-JR-3345 group.

A comparison of the pre-trial total symptomatology scores at the end of the first 8-week period showed a significant improvement ($p \leq .01$) (Wilcoxon and Sign-Ranks test). The total score then became significantly worse when medication was stopped for two weeks ($p > .05$) and again a significant improvement ($p = .01$) occurred during the second 8-week period of medication. This pattern was repeated in the third trial period, i.e. there was exacerbation of symptoms during the 2-week inter-trial medication-free period and a significant improvement ($p > .01$) in the total symptom rating scores for the third trial period on the drugs. These findings are presented in Figure XI.

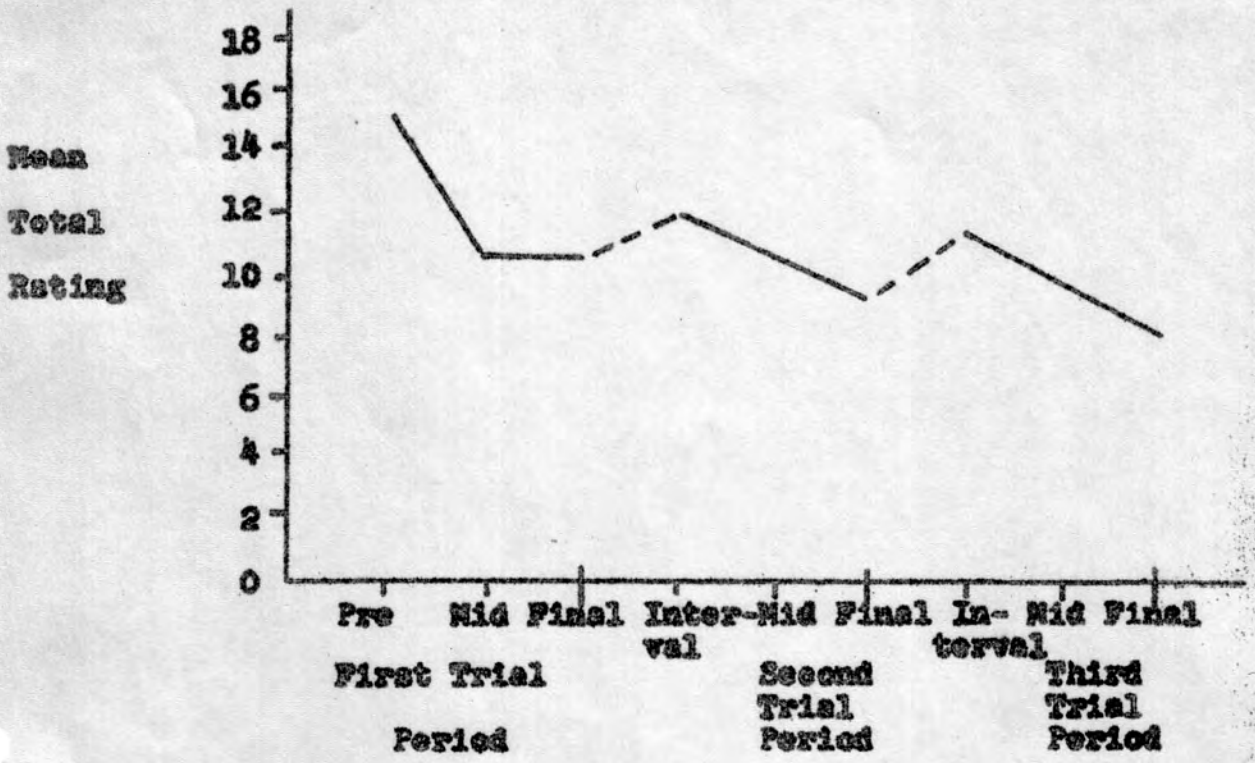


FIGURE XI.

A comparison for each drug between the pre-trial total symptom ratings and the ratings at the end of the 8-week period is presented in Figure XII.

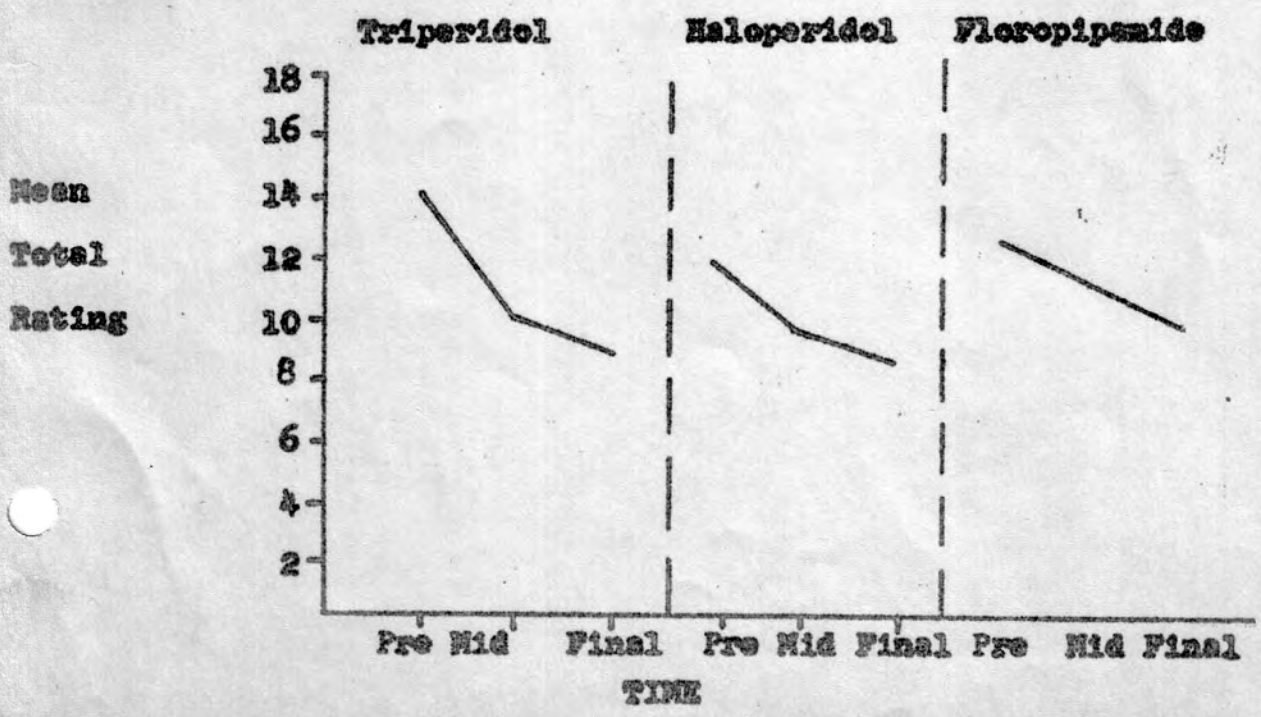


FIGURE XII.

The 3 drugs differed in the time required to effect a significant decrease of improvement in symptomatology. MeN-JR-2498 showed a significant improvement ($p < .01$) in the Target Symptom Scale for the pre-trial rate and the rating to the end of the 4th week. From the 4th to the 8th week there was a further but non-significant improvement in total symptom rating scales. R-1625 effected a less significant ($p \geq .05$) improvement for the first half of the trial period and a non-significant improvement for the second half of the trial. A further improvement from the pre-trial to final ratings was significant at the .01 level of confidence. A comparison of the pre- and mid-trial ratings for MeN-JR-3345 showed a non-significant improvement in symptoms which continued on this basis during the second half of the trial period. However in this case the total change from the pre-trial to the final ratings reached the .01 level of significance.

An analysis of these specific target symptoms showed that only certain symptoms were effected by the drug (Table XXII).

	MeN-JR-2498	R-1625	MeN-JR-3345
Excitement	p-0.008	N.S.	p-0.016
Suspiciousness	p-0.031	N.S.	N.S.
Hostility	no change	no change	no change
Anxiety	N.S.	no change	no change
Apathy	N.S.	N.S.	N.S.
Object Relations	p-0.016	N.S.	no change
Hallucinations	N.S.	N.S.	N.S.
Disturbance of Thinking	p-0.016	N.S.	N.S.
Delusions	N.S.	p-0.016	N.S.
Memory	no change	no change	no change
Consciousness	no change	no change	no change
Social Responses	N.S.	N.S.	N.S.

Table XXII.

MeN-JR-2498 brought about significant improvement in excitement ($p = .008$), suspiciousness ($p = .031$), object relations ($p = .016$), disturbance of thinking ($p = .016$). R-1625 effected a significant improvement in the symptom delusions ($p = .016$) and MeN-JR-3345 a significant improvement in the symptom of excitement ($p = .016$). No change was noted with respect to 'memory' and 'consciousness'. The ratings showed other symptoms improved, but not significantly.

Among the physical measures, with the exception of weight, there was no significant change observed during the trial period. Weight changes occurred with 2 of the compounds but in different directions. There was significant loss of weight in the patients on MeN-JR-2498 at the $p < .01$ level of confidence, while patients on MeN-JR-3345 gained weight significantly ($p < .05$).

Side effects with all 3 compounds occurred in general in the same areas (drowsiness, excessive salivation, rigidity, tremor, etc.). It should be noted that the number of side effects observed during the total trial period differed with each drug and was 32 in patients receiving McN-JR-2498, 24 for patients receiving R-1625 and 20 for patients receiving McN-JR-3345.

This drug trial was originally designed for 15 patients, but during the course of the experimental period 5 patients had to be dropped from the study. Findings presented above therefore are based on the findings with the remaining 10. Of the 5 cases mentioned, 4 were taken off medication while on McN-JR-2498 and 1 while on McN-JR-3345. Furthermore 4 of these 5 patients were taken off because of adverse physical or behavioral effects (depression with suicidal attempt, anxiety spells with marked dystonic and myoclonic seizures, akinetic syndrome with insomnia, incontinence and confusion). In the 5th case, her dramatic improvement resulted in a discharge from the hospital.

It should also be noted that in two McN-JR-2498 cases, marked liver toxicity was revealed (S.G.P.T. 200 and 102, S.G.O.T. 94 and 84 respectively).

Opinion: Order of antipsychotic potency: McN-JR-2498, R-1625 and McN-JR-3345. The same order of toxicity.

(Ban, T.A., Stonehill, E. and Lehmann, H.E. Butyrophenones in Psychiatry. Symposium, L'Annonciation, Quebec. January 10, 1964. In Press.)