

Reprinted from

JOURNAL OF THE HILLSIDE HOSPITAL

Volume V

April, 1956

Number 2

EVALUATION OF HIGH-DOSE RESERPINE THERAPY FOR RELIEF OF ANXIETY¹

MORTON WACHSPRESS, M.D.,² ARNOLD G. BLUMBERG, M.D.,³

MAX FINK, M.D.,⁴ and JOSEPH S. A. MILLER, M.D.⁵

During the past few years increasing interest has been shown in the role of drugs in psychiatric practice. Previous studies on the usefulness of extracts of *Rauwolfia Serpentina* at this hospital demonstrated minimal value for this drug in alleviating anxiety symptoms (4). In the light of these studies which contrasted with more recent enthusiastic reports, an investigation of the effectiveness of large doses of reserpine in relieving anxiety symptoms and altering behavior was undertaken.

Numerous reports have appeared in the past two years describing the effectiveness of reserpine in reducing aggressive and assaultive behavior (2, 5); alleviating manic states (14); and reducing the need for electroshock therapy (10). The reports of its potency in reducing anxiety, affecting neurotic symptoms or altering depressive symptoms (6, 12) have been less laudatory. In addition, reserpine-induced depressions have been noted in the course of treatment for hypertension (9, 11). No evidence has been forthcoming that reserpine has altered the course of a psychiatric illness, although many reports emphasize the quieting effects of the drug or its usefulness as an "adjuvant to psychotherapy" (7).

This investigation was undertaken to determine the usefulness of reserpine in a voluntary psychiatric hospital population treated in an open ward setting. A double-blind placebo controlled study with

¹ From the Research Service and Medical Department of the Hillside Hospital, Glen Oaks, N. Y.

² Senior Resident Psychiatrist, Hillside Hospital, Glen Oaks, N. Y.

³ Associate Visiting Physician, Hillside Hospital, Glen Oaks, N. Y.

⁴ Director of Research, Hillside Hospital, Glen Oaks, N. Y.

⁵ Medical Director, Hillside Hospital, Glen Oaks, N. Y.

large fixed doses of drug was selected as a technic of evaluation for this study. The evaluation of improvement in a psychiatric patient under therapy presents problems which are all too familiar to careful investigators in the field. In a hospital environment where the total therapeutic regime combines to produce improvement, the evaluation of the effect of a drug must be carefully controlled. Certain criteria must be established to differentiate between improvement consistent with the course of the disease, and improvement greater than what may be expected from the normal course of hospitalization. To properly attribute improvement to a drug the following criteria should be satisfied: the patient should improve while receiving medication; this improvement should be greater than at the time when the medication is replaced by suitable placebo medication; and improvement should be reproducible at a later date with a similar drug dosage. The use of a double-blind placebo controlled study provides a method for such an evaluation and it is doubtful if definitive conclusions are justified in the absence of such studies (3).

To further minimize the subjective factor in the clinical evaluation, rating scales have been employed, despite their well-known limitations. In this study, the revised rating scale of Malamud and Sands (8) was utilized to provide further experience for the observers in standardizing their reports and to permit a constant frame of reference for changes in symptoms and behavior during therapy.

METHOD

The patients in this study were those who presented, both subjectively and objectively, severe anxiety and agitation. They were selected from the patients recommended by the resident psychiatrists for electroshock or drug therapy. The final decision as to which patients should receive reserpine was made by the two psychiatrists working on the study, who based their selection on the presence of severe anxiety and tension symptoms.

Of the original group of seventeen, fifteen patients completed the study. Two male patients, one diagnosed as schizophrenia and one as psychoneurosis, discontinued the treatment because of increasing tension, agitation and nausea while on the drug regimens. Of the seventeen patients, eleven were diagnosed as schizophrenia, five as psychotic depression and one as mixed psychoneurosis. There were eight males and nine females. The age range was 19 to 52 with a median age of thirty-three.

Each patient was observed for a period of twelve weeks. Every patient received an intramuscular injection of 2cc. of reserpine⁶ and five tablets daily throughout the twelve-week period. Depending on which regimen was selected, placebo tablets and injections were substituted for the drug.

The four regimens were:

- (1) reserpine, 10 mg. daily—5 mg. orally and 5 mg. intramuscular;
- (2) reserpine, 5 mg. daily—orally;
- (3) reserpine, 5 mg. daily—intramuscular; and
- (4) placebo only.

Regimens were selected in random order by the internist, and the regimen was unknown to the patient, therapist, evaluating psychiatrist or nursing personnel.

Weekly psychiatric evaluations were done on each patient by an evaluating psychiatrist. A modified Malamud scale was employed as well as the subjective reports of the patient and the impressions of the observer.

The patients were concurrently studied by the internist at regular intervals. Blood pressures and pulse rates were measured in a sitting position on casual examination at irregular intervals. Only two patients could be classified as hypertensive before treatment. Each patient was weighed weekly. A radioactive iodine determination was performed before starting treatment and repeated no sooner than three weeks after instituting treatment with an effective dose of reserpine. Routine blood counts, urinalyses and other laboratory tests were conducted as indicated.

RESULTS

Psychiatric Observations

Of the fifteen patients, seven showed a significant alteration in behavior which could be related to drug dosage. Of these, three showed a relief of anxiety and tension, and four, an increase in depression, tension and agitation. The remaining eight patients manifested no change in behavior. In addition, the two patients who discontinued the drug regimens did so because of an increase in tension and anxiety accompanied by nausea and vomiting.

⁶ We are indebted to the Ciba Pharmaceutical Company for the reserpine (Serpasil) and placebo medication used in this study.

total scores, an item analysis of the individual behavior items was undertaken. Those representative items were selected which clinical experience suggested might reveal changes due to drug action. The items chosen were: feeling, mood, motor activity, and thought processes. An analysis of these scores failed to indicate any consistent difference in these characteristics in the patients as a group.

Regarding the differences in the drug regimens, it was the clinical impression of the evaluating psychiatrists and resident therapists that more moderate doses of reserpine were preferable, giving fewer objectionable symptoms. Six of the fifteen patients were subjectively worse on the daily dose of 10 mg. These six included *A. S.*, one of the patients who improved on drug regimen, and two of the four patients whose condition became worse.

Toxic Symptoms

Of seventeen patients who started on the study, two stopped because of side effects. These patients manifested increased tension and anxiety, in which nausea and vomiting became prominent symptoms. Numerous other side effects were observed, and the incidence of each is noted in Table II. Drowsiness and dizziness were seen in most of the patients, but caused serious difficulty in none. Six

TABLE I
BEHAVIORAL RATINGS—TOTAL SCORE

	Sex	Age	Diagnosis	No Med- ication	Placebo	Oral	Intramus- cular	Com- bined
H.C.	F	24	Schiz.	27	20	15	17	28-34
G.W.	F	52	Invol. Mel.		27	50,53	38	25-42
F.S.	M	45	Schiz.	23-36	36-45	23,25	29-39	29-38
M.C.	F	19	Schiz.	20	16-22	27,26	18	20-31
R.S.	F	19	Schiz.	35,36	27,25	26	22,15	23,27
R.D.	M	20	Schiz.	30,35	27-38	40	47,31	28-36
A.S.	F	46	Invol. Mel.		6-9	15,3	12,13	12,15
F.G.	F	28	Schiz.	37-46	23-43	45,31	37,39	29-40
S.G.	F	37	M.D.D.	29-35	16-30	25,28	27	20
L.E.	M	50	M.D.D.	34,30	18-29	27	34	29
M.D.	F	42	Invol. Mel.	12-19	18,9	8-25	16-28	19
S.K.	F	37	Schiz.		19-33	28	20-26	25-38
P.M.	M	22	Schiz.		26-28	27	18-26	16-30
A.L.	M	37	Schiz.	53	46-57	53	53	51-56
M.B.	M	22	Schiz.	51,64	57,66	44,61	32-51	63-55

patients developed a Parkinsonian muscular rigidity, which disappeared within a few days after the drug was discontinued. Four patients had one or more episodes of generalized flushing lasting up to twenty-four hours. This occurred in patients on placebo as well as on drug, and was interpreted as an allergic reaction to impurities in the intramuscular solution.

TABLE II
TOXIC EFFECTS

	Incidence
Drowsiness	14
Stuffy nose	13
Dizziness and Weakness	10
Nausea	7*
Parkinsonism	6
Painful legs	4
Hot flashes	4
Restlessness	3
Swollen feet	1

* In 2 patients nausea was accompanied by vomiting and was a factor in discontinuing treatment.

Depression

The enhancement of existing depressive symptoms was noted in three patients, and in another, depressive symptoms appeared where none had been evident before reserpine therapy. In each instance, electroshock therapy was recommended and improvement resulted. Electroshock therapy induced a remission of the anxiety and tension components of the illness, as well as the depressive. Of the eight patients who manifested no change with reserpine, two were eventually treated with electroshock, without clinical improvement.

Physiologic Observations

The systolic blood pressure was reduced in fifteen of the sixteen patients observed over an extended period of time. The magnitude of this lowering was between 10 and 20 mm. Systolic blood pressures between 90 and 100 mm. were not unusual while on treatment and were not accompanied by adverse symptoms.

Table III represents average figures for the highest and lowest blood pressure and pulse rate recorded during each regimen. There

is a significant drop in both systolic and diastolic blood pressure and in pulse rate with reserpine therapy. There is no difference in the hypotensive or bradycardiac effect of intramuscular or oral administration of 5 mg. reserpine; nor is there any indication that a dosage of 10 mg. produces a greater effect on blood pressure or pulse rate than 5 mg. These observations are consistent with previous reports of the flat dose response curve for reserpine (1).

TABLE III

Medication	Range Systolic Pressure	Range Diastolic Pressure	Range Pulse Rate
Placebo	135-117	84-69	98-78
5 mg. p.o.	116-108	70-64	74-67
5 mg. i.m.	118-106	71-63	74-68
10 mg. combined	119-109	68-61	78-68

Most patients on reserpine reported an increase in appetite, and there was a tendency for these patients to gain weight. In seven patients, such gains varied from 3 to 20 pounds on the entire treatment program. Three patients lost weight and four showed no change.

There was no consistent change in the radioactive iodine (I-131) uptake following the administration of reserpine. Nor could a correlation between weight change and this index be found. Thus, only two of the patients who gained weight had a decrease in the iodine uptake. One patient who lost weight had a rise in iodine uptake. It was concluded that the weight gain and increased appetite were not related to alteration in thyroid function.

DISCUSSION

High-dose reserpine therapy did not affect the symptoms of anxiety or tension in these patients. For the most part, patients were made uncomfortable by the high doses used in this study. Of the three instances where a relationship between changes in anxiety and tension could be related to drug dosage, two were noted in severely ill patients in whom overactivity and agitation were first controlled. The relief of anxiety was secondary to the decrease in motor excitement. The previous study at this hospital demonstrated the limited usefulness of low-dosage reserpine therapy for the relief of anxiety. Considering this, and the results of the present study of

high-dosage reserpine, it may be concluded that reserpine therapy, either in low or high doses, has limited use for its relief of anxiety symptoms in this hospital's population. Its use is further limited by the exacerbation in depression which was observed.

Our observations, however, tend to support the reported usefulness of this medication as a sedative in the control of destructive and overactive behavior. This is seen in our two cases (*R. S.*, *M. B.*) and in a series of other overactive patients at the hospital who were noted to respond to the sedative action of reserpine when this was introduced in lieu of restraints and massive sedation.

The doses of reserpine in this study were generally too high. Patients were unable to tolerate 10 mg. without uncomfortable side effects. In no instance were the side effects severe or disabling, however, and in each instance the symptoms responded to a decrease in drug dosage. The symptom of depression, however, has assumed special significance in these patients. Reserpine exaggerated this symptom and, in one instance, elicited a depression with suicidal trends. The reports of increased depression (9, 11) are thus confirmed; and the usefulness of electroshock therapy in relieving these depressions can be re-emphasized. In this regard, the earlier enthusiastic reports of the usefulness of reserpine as a substitute for electroshock therapy (10) need reassessment. Reserpine is no substitute for electroshock therapy in the treatment of depressive states. It may substitute, however, for the use of electroshock as a sedative in the management of overactive and assaultive behavior.

This study exemplifies the advantages and disadvantages of a drug evaluation study by the double-blind placebo method. With a limited number of subjects, it is possible to obtain a meaningful evaluation of the primary effects and complications of a medication. The drug effects may also be separated from the natural course of the illness, and from the investment of the therapist in the conclusions. Such a technic has the following limitations: rigidity of dosage; inability of the therapist to separate drug-induced effects from alterations in the disease process during the study period; and the necessity of the selection of patients who are tractable and can tolerate discomfort for extended periods. Furthermore, such a study may rob the therapist of his faith in the drug as a therapeutic vehicle, and thereby limit the patient's response to the physiologic effects alone. It also limits the therapist's control over the care of his patient, and thereby arouses feelings of helplessness and apprehension in the therapist. In such instances, the cooperation of a mature

therapist is essential because there is considerable opportunity for the manipulating, demanding, and paranoid patient to arouse the therapist's anxiety and hostility to the experimental program.

This study also provided an opportunity to assess the usefulness of rating scales. In assessing the changes seen during treatment the rating scales failed to provide any information not available in the descriptive statements. They did provide, however, a frame of reference for the many items of the psychiatric interview that needed rating, and provided a base for the comparison of observations made by different observers.

SUMMARY AND CONCLUSIONS

In a double-blind placebo evaluation of 5 mg. and 10 mg. doses of oral and intramuscular reserpine, fifteen voluntary hospitalized psychiatric patients with severe, overt symptoms of anxiety were studied. Three patients manifested relief of anxiety related to drug dosage. In twelve patients no relief was noted, and of these, four exhibited severe depressive reactions which eventually responded to electroshock therapy.

Cardiovascular effects of high doses of reserpine were not significantly different than previously reported effects of low dosage. There was no evidence that reserpine altered thyroid function, although weight gain frequently occurred.

The usefulness of high-dose reserpine therapy in the relief of anxiety symptoms is limited. The dangers of induced depressions, as well as the rationale of placebo studies and psychiatric rating scales are discussed.

REFERENCES

- (1) A. M. A. Report of Council On Pharmacy and Chemistry, *J. A. M. A.*, 159:1206, 1955.
- (2) Barsa, J. A. and Kline, N. S.: Treatment of Two Hundred Disturbed Psychotics with Reserpine. *J. A. M. A.*, 158:110, 1955.
- (3) Beecher, H. K.: The Powerful Placebo. *J. A. M. A.*, 159:1602, 1955.
- (4) Blumberg, A. G., Cohen, L., and Miller, J. S. A.: The Effect of Rauwolfia Serpentina on Anxiety States. *This Journal*, 3:140-146, 1954.
- (5) Cowden, R. C., Zax, M., and Sproles, J. A.: Reserpine—Alone and as an Adjuvant to Psychotherapy in the Treatment of Schizophrenia. *A. M. A. Arch. Neurol. & Psychiat.*, 74:518-522, 1955.
- (6) Drake, F. R. and Ebaugh, R. G.: The Use of Reserpine in Office Psychiatry: Preliminary Report. *Ann. N. Y. Acad. Sci.*, 61:198, 1955.
- (7) Hoffman, J. L. and Konchegul, L.: Clinical and Psychological Observations on Psychiatric Patients Treated with Reserpine: A Preliminary Report. *Ann. N. Y. Acad. Sci.*, 61:144, 1955.

- (8) Malamud, W. and Sands, S. L.: A Revision of the Psychiatric Rating Scale. *Am. J. Psychiat.*, 104:231, 1947.
- (9) Muller, J. C., Pryor, W. W., Gibbons, J. E., and Orgain, E. S.: Depression and Anxiety Occurring During Rauwolfia Therapy. *J. A. M. A.*, 159:836, 1955.
- (10) Noce, H., Williams, B., and Rapaport, W.: Reserpine (Serpasil) in the Management of the Mentally Ill. *J. A. M. A.*, 158:11, 1955.
- (11) Schroeder, H. A. and Perry, H. M.: Psychoses Apparently Produced by Reserpine. *J. A. M. A.*, 159:839, 1955.
- (12) Smith, S. K.: The Use of Reserpine in Private Psychiatric Practice. *Ann. N. Y. Acad. Sci.*, 61:206, 1955.
- (13) Wilcoxon, F.: *Some Rapid Approximate Statistical Procedures*. New York: Am. Cyanamid Co., 1949.
- (14) Zeller, W. W., Graffagnino, P. N., Cullen, C. F. and Rietman, H. J.: Use of Chlorpromazine and Reserpine in the Treatment of Emotional Disorders. *J. A. M. A.*, 160:179, 1956.

Evaluation of High-Dose Reserpine Therapy for Relief of Anxiety

Morton Wachspress, M.D. (1)

Arnold G. Blumberg, M.D. (2)

Max Fink, M.D. (3)

Joseph S. A. Miller, M.D. (4)

From the Research Service and Medical Department of the Hillside Hospital,
Glen Oaks, New York.

- (1) Senior Resident Psychiatrist
- (2) Associate Attending Internist
- (3) Director of Research
- (4) Medical Director

Submitted to J. Hillside Hospital, 3-2-56

During the past few years increasing interest has been shown in the role of drugs in psychiatric practice. Previous studies on the usefulness of extracts of Rauwolfia Serpentina at this hospital demonstrated minimal value for this drug in alleviating anxiety symptoms. (1) In the light of these studies which contrasted with more recent enthusiastic reports, an investigation of the effectiveness of large doses of reserpine in relieving anxiety symptoms and altering behavior was undertaken.

Numerous reports have appeared in the past two years describing the effectiveness of reserpine in reducing aggressive and assaultive behavior (2); alleviating manic states (3); and reducing the need for electroshock therapy (4). The reports of its potency in reducing anxiety, affecting neurotic symptoms or altering depressive symptoms (5) have been less laudatory. In addition, reserpine induced depressions have been noted in the course of treatment for hypertension (6). No evidence has been forthcoming that reserpine has altered the course of a psychiatric illness, although many reports emphasize the quieting effects of the drug or its usefulness as an "adjuvant to psychotherapy" (7).

This investigation was undertaken to determine the usefulness of reserpine in a voluntary psychiatric hospital population treated in an open ward setting. A double-blind placebo controlled study with large fixed doses of drug was selected as a technic of evaluation for this study. The evaluation of improvement in a psychiatric patient under therapy presents problems which are all too familiar to careful investigators in the field. In a hospital environment where the total therapeutic regime combines to produce improvement, the evaluation of the effect of a drug must be carefully controlled. Certain criteria must be established to differentiate between improvement consistent with the course of the disease, and improvement greater than what may be expected from the normal course of hospitalization. To properly attribute improvement to a drug the following criteria should be satisfied: The patient should improve while receiving medi-

cation; this improvement should be greater than at the time when the medication is replaced by suitable placebo medication; and improvement should be reproducible at a later date with a similar drug dosage. The use of a double-blind placebo controlled study provides a method for such an evaluation and it is doubtful if definitive conclusions are justified in the absence of such studies (8).

To further minimize the subjective factor in the clinical evaluation, rating scales have been employed, despite their well known limitations. In this study, the revised rating scale of Malamud and Sands (9) was utilized to provide further experience for the observers in standardizing their reports and permit a constant frame of reference for changes in symptoms and behavior during therapy.

Method:

The patients in this study were those who presented, both subjectively and objectively, severe anxiety and agitation. They were selected from the patients recommended by the resident psychiatrists for electroshock or drug therapy. The final decision as to which patients should receive reserpine was made by the two psychiatrists working on the study, who based their selection on the presence of severe anxiety and tension symptoms.

Of the original group of seventeen, fifteen patients completed the study. Two male patients, one diagnosed as schizophrenia and one as psychoneurosis, discontinued the treatment because of increasing tension, agitation and nausea while on the drug regimens. Of the patients, eleven were diagnosed as schizophrenia, five as psychotic depression and one as mixed psychoneurosis. There were 8 males and 9 females. The age range was 19 to 52 with a median age of 33.

Each patient was observed for a period of 12 weeks. Every patient received an intramuscular injection of 2cc. of reserpine* and 5 tablets daily throughout the 12 week period. Depending on which regimen was selected, placebo tablets and injections were substituted for the drug.

The 4 regimens were:

- (1) reserpine, 10 mg. daily - 5 mg. orally and 5 mg. intramuscular;
- (2) reserpine, 5 mg. daily - orally;
- (3) reserpine, 5 mg. daily - intramuscular; and
- (4) placebo only.

Regimens were selected in random order by the internist, and the regimen was unknown to the patient, therapist, evaluating psychiatrist or nursing personnel.

Weekly psychiatric evaluations were done on each patient by an evaluating psychiatrist. A modified Malamud scale was employed as well as the subjective reports of the patient and the impressions of the observer.

* We are indebted to the Ciba Pharmaceutical Company for the reserpine (Serpasil) and placebo medication needed in this study.

The patients were concurrently studied by the internist at regular intervals. Blood pressures and pulse rates were measured in a sitting position on casual examination at irregular intervals. Only two patients could be classified as hypertensive before treatment. Each patient was weighed weekly. A radioactive iodine determination was performed before starting treatment and repeated no sooner than 3 weeks after instituting treatment with an effective dose of reserpine. Routine blood counts, urinalyses and other laboratory tests were conducted as indicated.

Results:

Psychiatric Observations:

Of the fifteen patients, seven showed a significant alteration in behavior during the drug regimens which could be related to drug dosage. Of these, three showed a relief of anxiety and tension, and four, an increase in depression, tension and agitation. The remaining eight patients manifested no change in behavior. In addition, the two patients who discontinued the drug regimens did so because of an increase in tension and anxiety accompanied by nausea and vomiting.

In the improved patients, an alleviation of anxiety was apparent and related to drug administration. M.B., a 22 year old male diagnosed as paranoid schizophrenia, was anxious, depressed, withdrawn, blocked, delusional and hallucinating. He had been hospitalized for three of the previous five years, and had received courses of insulin coma and electroshock therapy with only transient periods of improvement. After five months of hospitalization at Hillside Hospital he showed no improvement. During the drug regimens, there was a diminution in his anxiety, depression, agitation and preoccupation with delusions. These symptoms recurred when on placebo medication. Introduction of the drug regimen again resulted in the alleviation of these symptoms, with the progressive amelioration of his depressive feelings. With the reduction of his drug dosage to 5 mg. oral, he again manifested a recurrence of symptoms, only to have them relieved by the combined (10 mg.) regimen. The patient was maintained on this treatment and discharged, improved, six months after the treatment was instituted.

A.S., a 46 year old hypertensive woman, manifested severe tension, anxiety, depression, tremulousness and insomnia, which had fluctuated over a 2 year period. Her diagnosis was involuntional melancholia. While on 5 mg. drug regimens, there was considerable relief of anxiety with a decrease in tremulousness. Insomnia became less, but her depression was unaffected. Placebo regimen resulted

in a recrudescence of her symptoms. The combined (10 mg.) drug regimen increased the feelings of depression, induced somatic complaints and failed to abate the anxiety. A lowering of her medication to 5 mg. resulted in a repetition of the period of relief of anxiety and tremulousness. The patient was discharged, improved, on this dose of oral reserpine.

R.S., a 19 year old girl with hebephrenic schizophrenia, was overactive, anxious, tense, fearful, and manifested both ideas of reference and auditory hallucinations. Electroshock and insulin coma therapy afforded her only transient relief. While on 5 mg. drug regimens, she became less active, less anxious but more depressed. Her dress became bizarre. When placebo medication was introduced, her hallucinations ceased, her anxiety was more manifest but the depressive features were less. On combined drug regimen, she became calmer, more controlled in her behavior, but the bizarre appearance and ideational disturbances persisted.

In these three cases, a relationship between drug regimens and the relief of anxiety symptoms could be demonstrated. In both M.B. and R.S., the overt manifestations of severe schizophrenia were sufficiently modified to permit participation by the patient in milieu and psychotherapeutic programs. In the other twelve cases, no such relationship could be demonstrated.

Of the four cases in whom the drug regimen induced increased symptoms, each manifested severe depressive feelings, crying spells and in one, suicidal preoccupations. The following case exemplified the group.

G.W., a 52 year old single woman, was admitted with a 7 year history of depression and hypochondriasis. A previous course of electroshock therapy was not completed because of injuries sustained in a fall. She was tense, anxious, tremulous and depressed. While on drug regimens she became more depressed and retarded. Her anxiety and agitation increased. With placebo medication there was some amelioration of these symptoms. Electroshock therapy was instituted.

She received 15 treatments, with a rapid relief of her tension, anxiety and depression. She was discharged one month later much improved.

There were eight patients in whom the drug regimen or placebo periods were indistinguishable. There was neither a relief nor an exaggeration of symptoms. The following case history illustrates the group.

F.G., a 28 year old woman, had a two year history of severe anxiety, tension, feelings of depersonalization and obsessive ruminations which followed the birth of her first child. She had previously been treated with insulin coma and three courses of electroshock therapy, with only transient relief. During the periods of reserpine study, she showed no change in her symptoms while on drug or placebo regimens.

The changes in behavior determined by psychiatric interviews and rated according to the Malamud scale are represented in Table I. In these tables, the figures represent the total scores for each observation period. The higher scores indicate deviation from more "normal" behavior. The "control period" is a period of observation without any drug medication. While the table lists the different regimens in a definite sequence, the actual sequence varied from patient to patient, in a random fashion. A statistical study, using Wilcoxon's method of paired replicates, (10) demonstrates no significant difference in the group between any of the drug or no-drug periods.

Because no significant change was demonstrated in the study of total scores, an item analysis of the individual behavior items was undertaken. Those representative items were selected which clinical experience suggested might reveal changes due to drug action. The items chosen were: feeling, mood, motor activity and thought processes. An analysis of these scores failed to indicate any consistent difference in these characteristics in the patients as a group.

Regarding the differences in the drug regimens, it was the clinical impression of the evaluating psychiatrists and resident therapists that more moder-

TABLE I

BEHAVIORAL RATINGS - TOTAL SCORE

	SEX	AGE	DIAGNOSIS	NO MEDICATION	PLACEBO	ORAL	INTRAMUSCULAR	COMBINED
H.C.	F	24	Schiz.	27	20	15	17	28-34
G.W.	F	52	Invol. Mel.		27	50,53	38	25-42
F.S.	M	45	Schiz.	23-36	36-45	23,25	29-39	29-38
M.C.	F	19	Schiz.	20	16-22	27,26	18	20-31
R.S.	F	19	Schiz.	35,36	27,25	26	22,15	23,27
R.D.	M	20	Schiz.	30,35	27-38	40	47,31	28-36
A.S.	F	46	Invol. Mel.		6-9	15,3	12,13	12,15
F.B.	F	28	Schiz.	37-46	23-43	45,31	37,39	29-40
S.G.	F	37	M.D.D.	29-35	16-30	25,28	27	20
L.E.	M	50	M.D.D.	34,30	18-29	27	34	29
H.D.	F	42	Invol. Mel.	12-19	18,9	8-25	16-28	19
S.K.	F	37	Schiz.		19-33	28	20-26	25-38
P.H.	M	22	Schiz.		26-28	27	18-26	16-30
A.L.	M	37	Schiz.	53	46-57	53	53	51-56
H.B.	M	22	Schiz.	51,64	57,66	44,61	32-51	63,55

ate doses of reserpine were preferable, giving fewer objectionable symptoms. Six of the fifteen patients were subjectively worse on the daily dose of 10 mg. These six included A. S., one of the patients who improved on drug regimen, and two of the four patients whose condition became worse.

Toxic Symptoms:

Of seventeen patients who started on the study, two stopped because of side effects. These patients manifested increased tension and anxiety, in which nausea and vomiting became prominent symptoms. Numerous other side effects were observed, and the incidence of each is noted in Table II. Drowsiness and dizziness were seen in most of the patients, but caused serious difficulty in none. Six patients developed a Parkinsonian muscular rigidity, which disappeared within a few days after the drug was discontinued. Four patients had one or more episodes of generalized flushing lasting up to 24 hours. This occurred in patients on placebo as well as on drug, and was interpreted as an allergic reaction to impurities in the intramuscular solution.

TABLE II

TOXIC EFFECTS

	INCIDENCE
Drowsiness	14
Dizziness and Weakness	10
Hot flashes	4
Swollen feet	1
Nausea	7*
Restlessness	3
Parkinsonism	6
Painful Legs	4
Stuffy nose	13

* In 2 patients nausea was accompanied by vomiting and was a factor in discontinuing treatment.

Depression:

The enhancement of existing depressive symptoms was noted in three patients, and in another, depressive symptoms appeared where none had been evident before reserpine therapy. In each instance, electroshock therapy was recommended and improvement resulted. Electroshock therapy induced a remission of the anxiety and tension components of the illness, as well as the depressive. Of the eight patients who manifested no change with reserpine, two were eventually treated with electroshock, without clinical improvement.

Physiologic Observations:

The systolic pressure was reduced in fifteen of the sixteen patients observed over an extended period of time. The magnitude of this lowering was between 10 and 20 mm. Systolic blood pressures between 90 and 100 mm. were not unusual while on treatment and were not accompanied by adverse symptoms.

Table III represents average figures for the highest and lowest blood pressure and pulse rate recorded during each regimen. There is a significant drop in both systolic and diastolic blood pressure and in pulse rate with reserpine therapy. There is no difference in the hypotensive or bradycardiac effect of intramuscular or oral administration of 5 mg. reserpine; nor is there any indication that a dosage of 10 mg. produces a greater effect on blood pressure or pulse rate than 5 mg. These observations are consistent with previous reports of the flat dose response curve for reserpine (11).

TABLE III

<u>MEDICATION</u>	<u>RANGE SYSTOLIC PRESSURE</u>	<u>RANGE DIASTOLIC PRESSURE</u>	<u>RANGE PULSE RATE</u>
Placebo	135-117	84-69	98-78
5 mg. p.o.	116-108	70-64	74-67
5 mg. i.m.	118-106	71-63	74-68
10 mg. combined	119-109	68-61	78-68

Most patients on reserpine reported an increase in appetite, and there was a tendency for these patients to gain weight. In seven patients, such gains varied from three to twenty pounds on the entire treatment program. Three patients lost weight and four showed no change.

There was no consistent change in the radioactive iodine (I-131) uptake following the administration of reserpine. Nor could a correlation between weight change and this index be found. Thus, only two of the patients who gained weight had a decrease in the iodine uptake. One patient who lost weight had a rise in iodine uptake. It was concluded that the weight gain and increased appetite was not related to alteration in thyroid function.

Discussion:

High dose reserpine therapy did not affect the symptoms of anxiety or tension in these patients. For the most part, patients were made uncomfortable by the high doses used in this study. Of the three instances where a relationship between changes in anxiety and tension could be related to drug dosage, two were noted in severely ill patients in whom overactivity and agitation were first controlled. The relief of anxiety was secondary to the decrease in motor excitement. The previous study at this hospital demonstrated the limited usefulness of low dosage reserpine therapy for the relief of anxiety. Considering this, and the results of the present study of high dosage reserpine, it may be concluded, that reserpine therapy, either in low or high doses, has limited use for its relief of anxiety symptoms in the hospital's population. Its use is further limited by the exacerbation in depression which was observed.

Our observations, however, tend to support the reported usefulness of this medication as a sedative in the control of destructive and overactive behavior. This is seen in our two cases (R.S., M.B.) and in a series of other overactive patients at the hospital who were noted to respond to the sedative action of reserpine when this was introduced in lieu of restraints and massive sedation.

The doses of reserpine in this study were generally too high. Patients were unable to tolerate 10 mg. without uncomfortable side effects. In no instance were the side effects severe or disabling, however, and in each instance the symptoms responded to a decrease in drug dosage. The symptom of depression, however, has assumed special significance in these patients. Reserpine exaggerated this symptom and in one instance, elicited a depression of suicidal proportions. The reports of increased depression (6) are thus confirmed; and the usefulness of electroshock therapy in relieving these depressions can be re-emphasized. In this regard, the earlier enthusiastic reports of the usefulness of reserpine as a sub-

stitute for electroshock therapy (4) needs re-assessment. Reserpine is no substitute for electroshock therapy in the treatment of depressive states. It may substitute, however, for the use of electroshock, as a sedative in the management of over-active and assaultive behavior.

This study exemplifies the advantages and disadvantages of a drug evaluation study by the double-blind placebo method. With a limited number of subjects, it is possible to obtain a meaningful evaluation of the primary effects and complications of a medication. The drug effects may also be separated from the natural course of the disease, and from the investment of the therapist in the conclusions. Such a technic has the following limitations: rigidity of dosage; inability of the therapist to separate drug induced effects from alterations in the disease process during the study period; and the necessity of the selection of patients who are tractable and can tolerate discomfort for extended periods. Furthermore, such a study may rob the therapist of his faith in the drug as a therapeutic vehicle, and thereby limit the patient's response to the physiologic effects alone. It also limits the therapist's control over the care of his patient, and thereby arouses in the therapist, feelings of helplessness and apprehension. In such instances, the cooperation of a mature therapist is essential as there is considerable opportunity for the manipulating, demanding, and paranoid patient to arouse the therapist's anxiety and hostility to the experimental program.

This study also provided an opportunity to assess the usefulness of rating scales in such an evaluation study. In assessing the changes seen during treatment the rating scales failed to provide any information not available in the descriptive statements. They did provide, however, a frame of reference for the many items of the psychiatric interview that needed rating, and provided a base for the comparison of observations made by different observers.

SUMMARY AND CONCLUSIONS

In a double-blind, placebo evaluation of 5 mg. and 10 mg. doses of oral and intramuscular reserpine, fifteen voluntary hospitalized psychiatric patients with severe, overt symptoms of anxiety were studied. Three patients manifested relief of anxiety related to drug dosage. In twelve patients no relief was noted, and of these, four exhibited severe depressive reactions which eventually responded to electroshock therapy.

Cardiovascular effects of high doses of reserpine were not significantly different than previously reported effects of low dosage. There was no evidence that reserpine altered thyroid function, although weight gain frequently occurred.

The usefulness of high dose reserpine therapy in the relief of anxiety symptoms is limited. The dangers of induced depressions, as well as the rationale of placebo studies and psychiatric rating scales are discussed.

References:

1. Blumberg, A.G., Cohen, L., and Miller, J.S.A.: The Effect of Rauwolfia Serpentina on Anxiety States, *J. Hillside Hosp.* 3: 140-146, (July) 1954.
- 2a. Cowden, R.C., Zax, M., and Sproles, J.A.: Reserpine---Alone and as an Adjunct to Psychotherapy in the Treatment of Schizophrenia, *A.M.A. Archives of Neurol. and Psychiat.* 74: 518-522 (Nov.) 1955.
- 2b. Barsa, J.A. and Kline, N.S.: Treatment of Two Hundred Disturbed Psychotics with Reserpine, *J.A.M.A.*, 158: 110 (May) 1955.
3. Zeller, W.W., Graffagnino, P.N., Cullen, C.F. and Rietman, H.J.: Use of Chlorpromazine and Reserpine in the Treatment of Emotional Disorders, *J. A.M.A.*, 160: 179, (Jan) 1956.
4. Noce, H., Williams, B., and Rapaport, W. Reserpine (Serpasil) in the Management of the Mentally Ill, *J.A.M.A.*, 158: 11, (May) 1955.
- 5a. Drake, F.R. and Ebaugh, R.G.: The Use of Reserpine in Office Psychiatry: Preliminary Report, *Annals N.Y. Acad. Sci.*, 61: 198 (April) 1955.
- 5b. Smith, S.K.: The Use of Reserpine in Private Psychiatric Practice, *ibid.*: 206.
- 6a. Muller, J.C., Pryor, W.W., Gibbons, J.E., and Orgain, E.S.: Depression and Anxiety Occurring During Rauwolfia Therapy, *J.A.M.A.* 159: 836, (oct) 1955.
- 6b. Schroeder, H.A. and Perry, H.M.: Psychoses Apparently Produced by Reserpine, *J.A.M.A.* 159: 839 (Oct) 1955.
7. Hoffman, J. L. and Konchequl, L.: Clinical and Psychological Observations on Psychiatric Patients Treated with Reserpine: A Preliminary Report, *Annals N.Y. Acad. Sci.*, 61: 144 (April) 1955.
8. Beecher, H.K.: The Powerful Placebo, *J.A.M.A.* 159: 1602, (Dec) 1955.
9. Malamud, W. and Sands, S. L.: A Revision of the Psychiatric Rating Scale, *Am. J. Psychiat.* 104: 231, 1947.
10. Wilcoxon, F.: Some Rapid Approximate Statistical Procedures, *Amer. Cyanimid Co., N.Y.*, 1949.
11. A.M.A. Report of Council On Pharmacy and Chemistry, *J.A.M.A.* 159: 1206, (Nov.) 1955.

In the improved patients, an alleviation of anxiety was apparent and related to drug administration. *M. B.*, a 22-year-old male, diagnosed as paranoid schizophrenia, was anxious, depressed, withdrawn, blocked, delusional and hallucinating. He had been hospitalized for three of the previous five years, and had received courses of insulin coma and electroshock therapy with only transient periods of improvement. After five months of hospitalization at Hillside Hospital he showed no improvement. During the drug regimens, there was a diminution in his anxiety, depression, agitation and preoccupation with delusions. These symptoms recurred when on placebo medication. Introduction of the drug regimen again resulted in the alleviation of these symptoms, with the progressive amelioration of his depressive feelings. With the reduction of his drug dosage to 5 mg. oral, he again manifested a recurrence of symptoms, only to have them relieved by the combined (10 mg.) regimen. The patient was maintained on this treatment and discharged, improved, six months after the treatment was instituted.

A. S., a 46-year-old hypertensive woman, manifested severe tension, anxiety, depression, tremulousness and insomnia, which had fluctuated over a two-year period. Her diagnosis was involuntional melancholia. While on 5 mg. drug regimens, there was considerable relief of anxiety with a decrease in tremulousness. Insomnia became less, but her depression was unaffected. Placebo regimen resulted in a recrudescence of her symptoms. The combined (10 mg.) drug regimen increased the feelings of depression, induced somatic complaints and failed to abate the anxiety. A lowering of her medication to 5 mg. resulted in a repetition of the period of relief of anxiety and tremulousness. The patient was discharged, improved, on this dose of oral reserpine.

R. S., a 19-year-old girl with hebephrenic schizophrenia, was overactive, anxious, tense, fearful, and manifested both ideas of reference and auditory hallucinations. Electroshock and insulin coma therapy afforded her only transient relief. While on 5 mg. drug regimens, she became less active, less anxious but more depressed. Her dress became bizarre. When placebo medication was introduced, her hallucinations ceased, her anxiety was more manifest but the depressive features were less. On combined drug regimen, she became calmer, more controlled in her behavior, but the bizarre appearance and ideational disturbances persisted.

In these three cases, a relationship between drug regimens and the relief of anxiety symptoms could be demonstrated. In both *M. B.*

and *R. S.*, the overt manifestations of severe schizophrenia were sufficiently modified to permit participation by the patient in milieu and psychotherapeutic programs. In the other twelve cases, no such relationship could be demonstrated.

Of the four cases in whom the drug regimen induced increased symptoms, each manifested severe depressive feelings, crying spells, and one, suicidal preoccupations. The following case exemplifies the group.

G. W., a 52-year-old single woman, was admitted with a seven-year history of depression and hypochondriasis. A previous course of electroshock therapy was not completed because of injuries sustained in a fall. She was tense, anxious, tremulous and depressed. While on drug regimens she became more depressed and retarded. Her anxiety and agitation increased. With placebo medication there was some amelioration of these symptoms. Electroshock therapy was instituted. She received fifteen treatments, with a rapid relief of her tension, anxiety and depression. She was discharged one month later, much improved.

There were eight patients in whom the drug regimen or placebo periods were indistinguishable. There was neither a relief nor an exaggeration of symptoms. The following case history illustrates the group.

F. G., a 28-year-old woman, had a two-year history of severe anxiety, tension, feelings of depersonalization and obsessive ruminations which followed the birth of her first child. She had previously been treated with insulin coma and three courses of electroshock therapy, with only transient relief. During the periods of reserpine study, she showed no change in her symptoms while on drug or placebo regimens.

The changes in behavior determined by psychiatric interviews and rated according to the Malamud scale are represented in Table I. In these tables, the figures represent the total scores for each observation period. The higher scores indicate deviation from more "normal" behavior. The "control period" is a period of observation without any drug medication. While the table lists the different regimens in a definite sequence, the actual sequence varied from patient to patient, in a random fashion. A statistical study, using Wilcoxon's method of paired replicates, (13) demonstrates no significant difference in the group between any of the drug or no-drug periods.

Because no significant change was demonstrated in the study of