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DEPRESSIVE STATES DURING RAUWOLFIA THERAPY FOR ARTERIAL HYPERTENSION*

A REPORT OF 30 CASES

GUY LEMIEUX, M.D.,
ANDRE DAVIGNON, M.D.† and
JACQUES GENEST, M.D., F.R.C.P., F.A.C.P.,
Montreal

DURING THE PAST YEAR, several reports[1-10] have appeared in the medical literature on the occurrence of mental symptoms during rauwolfia therapy for arterial hypertension. All these reports are concerned with only a very small number of patients, and the relationship between the occurrence of mental changes and the administration of rauwolfia has not been clearly established.

During the last 18 months, we have been able to observe 30 patients with depressive states during rauwolfia therapy for arterial hypertension. A study of these cases seems to indicate a definite relation between rauwolfia administration and mental symptoms.

Between June 1954 and December 1955, 296 patients were treated and seen regularly at our Hypertension Clinic. All these subjects had been previously admitted to the Hôtel-Dieu Hospital where a complete clinical investigation including evaluation of the cardiac, vascular, renal, cerebral and ophthalmoscopic status had been done in each case. After discharge, the patients were seen at weekly, fortnightly or monthly intervals.

Of these 296 patients (Table I) 101 took no rauwolfia preparations; they received either hydralazine (Apresoline), hexamethonium, or pentolinium (Ansolysen) alone or in combination.

The remaining 195 patients took rauwolfia preparations, either alone or in combination with the already mentioned drugs. Of these 195 patients, 134 subjects took reserpine (Serpasil, Serpiloid or Rau-Sed) and the remaining 61 took a whole root preparation (Raudixin) or the purified alkaloidal fraction also called the alseroxylon fraction (Rauwiloid).‡

TABLE I.

PATIENTS TREATED FOR ARTERIAL HYPERTENSION: JUNE 1954 - DECEMBER 1955

Total number of patients	296
Taking no rauwolfia	101
Taking rauwolfia†	195
Reserpine	134
Whole root or alseroxylon fraction	61

RESULTS

Among the 101 patients receiving no rauwolfia preparations, no subject developed any mental symptoms during therapy, whereas 30 out of the 195 patients under rauwolfia therapy showed a depressive state. Of these 30 patients, 24 were females and 6 were males. The age ranged from 33 to 70 years, with an average of 52.7 years. The clinical diagnosis of hypertensive state was as follows: essential hypertension 27 cases (18 benign, 4 severe and 5 arteriosclerotic), malignant hypertension 2 cases, and hypertension of renal origin 1 case (Table II).

The incidence of mental depression among the total number of patients is 10%. Fifteen per cent of all the patients receiving rauwolfia therapy had mental changes. Of the 30 patients who developed depressive states, 25 were under reserpine (83%)—18% of all subjects treated with this alkaloid. The remaining 5 were under whole root extract or alseroxylon fraction—8% of all patients treated with these agents.

The lapse of time between the administration of the drug and the appearance of mental symptoms is illustrated in Tables II and V. With reserpine, it ranged from 2 weeks to 14 months with an average of 4½ months. With the alseroxylon fraction, 5 months of therapy elapsed before the appearance of mental symptoms. When whole root extract was used, the lapse of time ranged from 2½ to 3 months with an average of almost 3 months.

The daily dosage of reserpine used ranged from 0.75 to 4 mg. and averaged 1.36 mg.; with the alseroxylon fraction, it ranged from 8 to 12 mg. and averaged 10 mg.; with the whole root extract, it ranged from 150 to 200 mg. with an average of 183 mg. (Tables II and V).

Clinically, the picture was that of mental depression, although two patients under reserpine (E.B. and W.L.) had definite psychotic reactions. The most frequent complaints were a

*From the Clinical Research Department, Hôtel-Dieu Hospital, Montreal. Work supported through grants from the Department of National Health and Welfare, Ottawa, and the Ministry of Health of Quebec (Federal-Provincial Plan) and the Ciba Company, Montreal.
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‡Rauwolfia preparations were kindly supplied to us through the courtesy of Dr. Walter Murphy, Ciba Co., Montreal (Serpasil); Mr. A. Garstone, Riker Pharmaceutical Co. Ltd. (Serpiloid and Rauwiloid), and Mr. J. H. Comte, E. R. Squibb & Sons of Canada Ltd. (Raudoxin and Rau-Sed).

TABLE II.

DEPRESSIVE STATES DURING RAUWOLFIA THERAPY

Patient	*Age*	*Sex*	*Arterial hypertension*	*Duration of therapy (months)*	*Daily dosage (mg.)*	*Severity of depression (grade I to IV) H = hospitalization*
					Reserpine	
R.L.	47	F.	Benign essential	6	1 - 2	II
F.R.	33	F.	Severe essential	3½	1	II
F.P.	43	F.	Malignant	3	0.75	IV
S.S.L.	70	F.	Arterioscl.	6½	1 - 1.5	II
N.A.L.	50	F.	Benign essential	½	4	III
V.K.	46	F.	Benign essential	6	0.5 - 1.5	III
G.M.	46	M.	Malignant	8	0.75 - 1.5	III
H.P.	63	F.	Severe essential	6	0.75	IV *H*
C.S.P.	53	F.	Benign essential	3	1.5	IV
L.P.	48	M.	Benign essential	5	1.5 - 3	IV *H*
E.B.	54	F.	Benign essential	7½	0.75 - 1.5	IV *H*
H.R.	56	F.	Benign essential	4	1.5 - 2	IV
C.R.	62	F.	Severe essential	4	1 - 1.5	III
P.L.	69	F.	Arterioscl.	3½	1 - 1.5	IV *H*
Y.H.	46	F.	Benign essential	4	1	IV
E.F.	56	F.	Benign essential	2	0.75	IV *H*
O.B.	58	M.	Benign essential	7	0.75 - 3	III *H*
J.E.L.	46	F.	Benign essential	6	2	IV *H*
E.S.	63	M.	Benign essential	4	1.5	II
I.M.	56	F.	Benign essential	½	1	III
E.R.	56	F.	Benign essential	5	1	III
A.L.	68	F.	Arterioscl.	½	1.5	III
D.R.	49	M.	Renal	2	0.75	IV *H*
W.L.	42	F.	Benign essential	3	0.75 - 1.5	IV *H*
E.P.	36	F.	Severe essential	14	0.75 - 1.5	III
					Alseroxylon Fr.	
J.P.	56	F.	Benign essential	5	12	IV *H*
P.B.	53	M.	Benign essential	5	8	II
					Whole root	
M.S.O.	38	F.	Benign essential	3	150 - 200	III
J.A.L.	55	F.	Arterioscl.	3	150 - 200	III
A.B.	64	F.	Arterioscl.	2½	200	III

TABLE III.

DEPRESSIVE STATES DURING THERAPY FOR ARTERIAL HYPERTENSION

Total number	30	100%
Taking no rauwolfia	0	0%
Taking rauwolfia	30	100%
Taking reserpine	25	83.3%
Taking the whole root	3	10%
Taking the alseroxylon fraction	2	6.6%

feeling of sadness and discouragement with lack of ambition and energy, crying spells without motivation, loss of interest in usual activities and worry over trifles (Table VI). Anxiety was not a constant feature, although it was definite in 9 cases. Other symptoms included weakness and fatigue, phobias, decreased appetite, insomnia,

TABLE IV.

INCIDENCE OF DEPRESSIVE STATES DURING RAUWOLFIA THERAPY

Total number (30 out of 296)	10%
Under rauwolfia (30 out of 195)	15%
Reserpine (25 out of 134)	18%
Whole root or alseroxylon fraction (5 out of 61)	8%

TABLE V.

DEPRESSIVE STATES DURING RAUWOLFIA THERAPY

	Average duration of therapy (months)	*Average daily dosage (mg.)*
Reserpine (25 cases)	4.5 (½ to 14)	1.36 (0.75 to 4)
Alseroxylon fraction (2 cases)	5	10 (8 to 12)
Whole root (3 cases)	2.8 (2½ to 3)	183 (150 to 200)

suicidal thoughts and vague somatic complaints. The two patients with psychotic reactions had agitation, mental confusion and delusions.

The severity of the mental syndrome was graded from I to IV depending on the intensity of symptoms (Table II). Only cases with definite mental changes are included in this series. Ten of the 30 cases required admission to the hospital and close psychiatric treatment. In these cases psychiatric diagnosis was as follows: depressive state 7, anxiety state 1, and melancholia 2. The other moderately severe cases received psychiat-

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TABLE VI.

DEPRESSIVE STATES DURING RAUWOLFIA THERAPY: SYMPTOMS (30 CASES)

Most frequent	*Less frequent*
Feeling of sadness and discouragement	Suicidal thoughts
Crying spells	Confusion
Loss of interest	Agitation
Worry over trifles	Delusions
Weakness and fatigue	Self-accusation
Phobias	Obsessive thinking
Anxiety	
Decreased appetite	
Vague somatic complaints	
Insomnia	

ric care in the outpatient clinic of the department of neuropsychiatry.

The management of the mental condition which developed under rauwolfia therapy is illustrated in Table VII. Complete cessation of administration of the drug in 19 cases resulted in total recovery in 11 patients, marked improvement in 7 and no improvement in 1 patient (P.L.) Reduction in dosage in 6 cases produced complete recovery in 4 cases, marked improvement in 1 and no effect in 1 subject (J.P.) who now manifests features of severe hypochondria. Electroshock therapy was administered to 5 patients with total recovery in 3 cases, marked improvement in 1 and no improvement in 1 patient (O.R.), who remains depressed and anxious after two courses of shock therapy.

TABLE VII.

MANAGEMENT OF DEPRESSIVE STATES DURING RAUWOLFIA THERAPY (30 CASES)

	Complete recovery	*Marked improvement*	*No improvement*
Complete cessation of the drug (19 cases).....	11	7	1
Reduction in dosage (6 cases)	4	1	1
Electroshock therapy (5 cases)	3	1	1

The period of time between the depressive state and recovery ranged from ½ to 3 months after cessation of the drug or reduction in dosage. Following electroshock therapy, recovery was much more rapid, demanding an average course of six treatments.

Seven patients who had developed a depressive state under reserpine therapy and who had completely recovered after cessation of the drug were again given reserpine at the former dosage. No relapse occurred in four patients after 1 to 4 months, while in the remaining three patients a relapse was noted 15 days to 2 months after resumption of reserpine; the mental symptoms disappeared rapidly with reduction in dosage.

Too much space would be needed to give an abstract of the history of each of our 30 cases. However, the following examples illustrate the clinical features of the depressive states encountered during rauwolfia therapy.

1. A 53-year-old woman (C.S.P.) with benign essential hypertension (average B.P. 210/110 mm. Hg) was given reserpine 1.5 mg. daily from July 27, 1954. Towards the end of August, she complained of occasional crying spells without motivation. On October 22, 1954, after three months of reserpine therapy, she began to feel depressed. She worried over trifles and complained of insomnia. There was no evident emotional problem and no history of previous mental depression. Reserpine was reduced to 1 mg. per day. On November 19, her depressive state became more accentuated. She felt sad and discouraged. She had crying spells without motivation every day. She complained of anorexia, loss of weight and insomnia; she stated that her food could not reach her stomach and she had much difficulty in swallowing. Complete x-ray studies of the digestive tract revealed no abnormality. The patient had lost interest in her previous activities; she could no longer read or pay attention to the radio or television. She also feared she was losing her mind, and that she had a serious disease such as cancer. On November 26, reserpine was reduced to 0.5 mg. per day, and amphetamine with mephenesin were given by the consulting psychiatrist.

By January 14, 1955, the mental symptoms had completely disappeared and the patient has been feeling well since then and is still taking 0.5 mg. reserpine a day.

2. A 48-year-old man (L.P.) with benign essential hypertension (average B.P. 230/140 mm. Hg) was given 300 mg. hydralazine and 1.5 mg. reserpine a day from August 6, 1954. Under this regimen, there was a significant lowering of the blood pressure to 180/110. On December 15, 1954, reserpine was increased to 3 mg. a day. On January 10, 1955, the patient was admitted to hospital in a severe depressive state. He felt like crying all the time; he also felt lonely and very sad. He was anxious, feared he would die suddenly and was afraid of walking alone. He complained of a feeling of pressure all over his head. Other complaints were of nausea, loss of appetite and inability to sleep well. The patient kept thinking of his parents and felt sorry for them because they were getting old. He had lost interest in reading or listening to the radio. He had a long history of emotional conflicts. Reserpine was ceased completely and a neuropsychiatrist was called in consultation. The patient improved rapidly with psychotherapy and amphetamine. On March 5, 1955, he was discharged on 100 mg. hydralazine a day. On March 18, 0.5 mg. reserpine a day was added. On April 15, the patient felt depressed again. Reserpine was discontinued and three weeks later the patient felt well with 400 mg. hydralazine a day. No relapse has occurred since then.

3. A 56-year-old woman (H.R.) with benign essential hypertension (average B.P. 240/120 mm. Hg) took 1.5 to 2 mg. reserpine daily from September 10, 1954, to January 7, 1955, at which time she developed a depressive state. She felt sad, discouraged, lonely and wished to remain alone. She also complained of insomnia and loss of interest in her previous activities. Reserpine was discontinued but the patient became progressively worse and psychotherapy provided no significant help. After a course of six electroshock treatments, the symptoms had completely disappeared. On March 4, 1955, reserpine was given again but at a lower dosage (0.5 mg. a day) with pentolinium and hydralazine. The patient has been well since.

4. A 62-year-old woman (C.R.) with severe essential hypertension (average B.P. 260/130 mm. Hg) took 1.5 mg. reserpine a day from September 24, 1954, to February 9, 1955. A depressive state then developed with crying spells, fatigue, worry over trifles, fear of staying alone and of losing her mind, and loss of interest in her previously enjoyed social activities. Reserpine was reduced to 0.75 mg. a day and on April 6, 1955, all the mental symptoms had disappeared with no relapse since then.

5. A 54-year-old woman (E.B.) with benign essential hypertension (average B.P. 220/120 mm. Hg) took 1.5 mg. reserpine a day during 7½ months, after which period an acute psychotic reaction developed. The patient felt sad and lonely and at times became agitated and confused. In the hospital, reserpine was reduced to 0.75 mg. per day and electroshock therapy was instituted. Three weeks later, she felt well and left the hospital. She has been taking 0.75 mg. reserpine a day since then, with no relapse.

DISCUSSION

We think that the present study of 30 cases of depressive states during rauwolfia therapy seems to clearly incriminate the latter drug in the production of mental symptoms. At first glance, reserpine seems to be the most active agent, as 83% of all our cases were under therapy with this drug and it may be logical to assume that the reserpine contained in the whole root extract or the alseroxylon fraction is responsible for these mental changes. However, the high incidence of mental depression during reserpine therapy may be due to the relatively much higher dosages used with this drug, as compared with whole root extract and the alseroxylon fraction. Had equivalent dosages of the latter drugs been used, the incidence of mental changes might have been the same during therapy with these agents. This aspect of the problem is now being studied at our clinic; reserpine is being given in doses of less than 0.6 mg. a day in order to find out whether the same hypotensive action can be obtained with a lower incidence of mental depression.

In evaluating the factors involved in the production of such mental changes, we could not detect any relationship between the hypotensive effect of rauwolfia and the occurrence of depressive states. It must also be remembered that in the 101 patients who received more potent hypotensive drugs like hydralazine, hexamethonium and pentolinium without rauwolfia, no depressive states were encountered.

The dosage used is certainly an important factor, for the average daily dosage in our patients exceeded that usually recommended; furthermore, reduction in dosage frequently resulted in complete recovery. However, many patients receiving larger doses of rauwolfia had no depressive symptoms, so that dosage cannot be considered as the sole important factor.

Duration of therapy averaged four months and seems to be another factor. But it must not be forgotten that some individuals developed a depressive state after only 15 days of therapy and some after periods of seven or even 14 months. Moreover, some patients have taken rauwolfia for 18 months and more without developing any mental depression.

The age of our patients might be another factor. The average age was 52.7 years, with the great majority past 50 years. Mental depression is mostly encountered in this age group, and rauwolfia might precipitate the development of mental depression during this period of life.

Individual susceptibility and pre-existing personality could well be another very important factor. Amongst our 30 patients 10 had evidently disturbed personality with apparent anxiety, features of hypochondria or a history of previous depressive moods and mental depression. Complete personality studies were made on only a few patients; we think that this factor should be thoroughly investigated during further studies.

We now feel that before instituting rauwolfia therapy in any case, a complete history regarding any previous mental depression or depressive moods should be obtained, especially if the patient is in the fifth decade of life or more. Rauwolfia preparations should be given with great caution if a tendency to mental depression is discovered. In any given case, the dosage prescribed should be as low as possible and probably under 0.75 mg. a day if reserpine is used. Other hypotensive agents should be resorted to, if rauwolfia fails to lower the blood pressure with this dosage.

SUMMARY AND CONCLUSIONS

1. During an 18-month period, 10% of all our patients treated for arterial hypertension developed a depressive state.

2. All these patients were under rauwolfia therapy.

3. The mental changes subsided after reduction in dosage or complete cessation of the drug, but sometimes required admission to hospital and electroshock therapy.

4. The most important factors in the production of these symptoms seem to be the dosage

used, the duration of therapy and probably the age, the susceptibility and the pre-existing personality of the patient.

5. Rauwolfia preparations should probably be given with great caution to patients with a previous history of mental depression, especially if they are in the fifth decade of life or more.

6. These agents should be used at the lowest effective dosage for the reduction of blood pressure. If reserpine is used, the dosage should be under 0.75 mg. a day.

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RÉSUMÉ

Les auteurs ont été à même de suivre une série de 296 hypertendus dont 195 recevaient une préparation quelconque de Rauwolfia. Alors qu'aucun des 101 ne recevant pas de Rauwolfia n'accusa de trouble mental, 30 de ceux qui en reçurent montrèrent un état dépressif. Ces symptômes se manifestèrent dans une moyenne d'environ 4 mois après le début du traitement. Les doses étaient supérieures à celles communément employées. Dix de ces malades durent être admis à l'hôpital pour y subir des traitements psychiatriques. La plupart s'améliorèrent, plusieurs même guérirent complètement à la simple diminution de la dose ou à la suppression de la Rauwolfia; cependant, un cas se montra rebelle à deux séries d'électrochocs. La thérapie fut reprise avec rechute dans certains cas et bonne tolérance dans d'autres. Il semblerait que l'âge des malades ainsi que les traits de leur personnalité soient des facteurs d'aussi grande importance dans le développement de ces troubles que les doses de médicament employées. M.R.D.

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PSYCHOSIS AND ENHANCED ANXIETY PRODUCED BY RESERPINE AND CHLORPROMAZINE*

G. J. SARWER-FONER, B.A., M.D. and W. OGLE, B.A., M.D., *Montreal*

WE FIRST REFERRED to the production of psychosis by reserpine and chlorpromazine in our preliminary report on the use of reserpine† in psychiatric patients.[8] Freis,[3] Doyle[2] and other authors[4, 5, 12] had previously mentioned mainly depressive reactions and an occasional anxiety reaction, as occurring in patients treated, on a long-term basis, with reserpine for essential hypertension. Recently, other authors[1, 6, 11] have reported psychotic depressions occurring during treatment for essential hypertension with reserpine. These latter authors have emphasized these reactions, whereas earlier authors, with the exception of Freis, had not done so. We believe our work to be the first dealing specifically with psychiatric patients, and offering an explanation of the mechanisms involved in these reactions. To our knowledge, it is also the first to implicate chlorpromazine as well as reserpine.

In a study of the physiological and psychological effects of reserpine on affect, 55 carefully selected psychiatric patients were intensively studied over a one-year period (July 1954 to July 1955). The research design was novel.[8, 9] The data and conclusions of this study have been reported in detail elsewhere.[8-10] Concomitantly chlorpromazine was used in 35 cases on a non-research basis, i.e. when indicated as an ordinary drug. Sixteen out of the above-mentioned groups are the subject of this paper, because they were characterized by the same general reaction types and by common psychodynamic elements. The present paper consists of a detailed report of these cases, a discussion of the factors involved, and a statement of how we believe this phenomenon is produced.

Dose: The average dose of reserpine in the 55 cases was 7 mg. daily orally or intramuscularly. The average duration of treatment was 26 days. For chlorpromazine the dose was 50-100 mg. three or four times a day orally or intramuscularly. Duration of treatment varied greatly in the 35 cases.

*From the Department of Psychiatry, Queen Mary Veterans Hospital, Montreal and the Department of Psychiatry, McGill University, Faculty of Medicine.

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