PAPERS AND ORIGINALS

L-Dopa in Parkinsonism and the Influence of Previous Thalamotomy

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British Medical Journal, 1971, 1, 7-13

Summary

A double-blind cross-over trial over 24 weeks (10 weeks on the active remedy, 4 weeks off treatment, and 10 weeks on placebo) of the effect of L-dopa on idiopathic Parkinsonism (paralysis agitans) has shown no difference in the response obtained in patients who had undergone previous stereotaxic ventrolateral thalamotomy and in those who had not. Of the 34 patients (18 men and 16 women) in the trial 18 had been operated on (nine unilateral, nine bilateral operations) and 16 had not. All patients entering the trial were taking anticholinergic drugs in stable dosage and these were continued throughout. The only factor which seemed to limit the response to treatment was pre-existing hypertension. Of 31 patients who completed the 10-week treatment period, 12 showed marked improvement, 15 moderate improvement, and 4 a mild or negligible change. It seems that previous ventrolateral thalamotomy affords some protection against the development of L-dopa-induced involuntary limb movements on the side contralateral to the operation. As found by others, maximum benefit was seen in bradykinesia and rigidity and related features but a significant reduction in tremor was also noted during treatment. Side effects (nausea, hypotension, and involuntary movements) were common but rarely limited the therapeutic response.

Introduction

Carlsson *et al.* (1957, 1958) showed that reserpine-induced dopamine depletion of the striatum in animals could be reversed by giving the laevo-isomer of the amino-acid 3, 4-

dihydroxyphenylalanine (L-dopa). Since Ehringer and Hornykiewicz (1960) found that this biogenic amine was depleted in the corpus striatum of patients with Parkinsonism, L-dopa has been widely used as a treatment for this disease. Initial trials with small doses parenterally or orally were encouraging (Birkmayer and Hornykiewicz, 1961; Barbeau, 1962), but some other results were less impressive (Greer and Williams, 1963; Rinaldi *et al.*, 1965). Since the enthusiastic reports of Cotzias *et al.* (1967), using larger doses, the beneficial effects of L-dopa in the idiopathic (Yahr *et al.* 1969), postencephalitic (Calne *et al.*, 1969), and toxic (Mena *et al.*, 1970) varieties of Parkinsonism have been amply confirmed. Akinesia, bradykinesia, and rigidity have been markedly improved, tremor and hypersalivation to a lesser extent; the effect on oculogyric crises and dystonia has been less consistent, but these features too have sometimes been improved (Mena *et al.*, 1970).

As many patients with Parkinsonism had previously been subjected to stereotaxic surgery, the present trial was designed to determine whether this in any way modified the response to L-dopa therapy. The response to such treatment in patients who had previously undergone either unilateral or bilateral stereotaxic thalamotomy was therefore compared with that in a similar group who had not been operated on.

Patients and Methods

Thirty-four patients (18 men and 16 women) with idiopathic Parkinsonism (paralysis agitans), aged from 46 to 72 years, in whom the duration of the disease varied from 3 to 27 years, were admitted to the trial; 18 had undergone stereotaxic surgery and 16 had not. Nine of the 18 "surgical" patients had had a unilateral operation and nine bilateral procedures; some patients had had repeat operations on one or other side.

Patients in whom akinesia, bradykinesia, and rigidity were the predominant clinical features were selected for both the surgical and the non-surgical group. As tremor was often absent or only mild or moderate in the "surgical" cases, no patients were included in the non-surgical group in whom tremor predominated, though some tremor was not a bar to inclusion.

Patients with severe hypertension (diastolic B.P. con-

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sistently >110 mm Hg), ischaemic heart disease, cardiac failure, or obvious dementia were excluded, as were those with postencephalitic, arteriosclerotic, toxic, or drug-induced Parkinsonism. On entry to the trial all patients had received a stable dose of standard anticholinergic remedies for at least six weeks.

The trial was conducted on an outpatient basis; it was of the double-blind cross-over type with two 10-week treatment periods; these were separated by a four-week treatment-free interval in order to minimize the "carry-over" effect of L-dopa. Patients were randomly allocated to drug or placebo groups so that at each stage about half of those in each group (no thalamotomy, unilateral thalamotomy, and bilateral thalamotomy) were receiving the active drug.

L-Dopa (Larodopa) 500-mg capsules and matching placebo capsules containing lactose were used throughout, the dose being increased by 1 g each week (0.5 g every three or four days) until either dose-limiting side effects occurred or a maximum daily dose of 6 g was reached after six weeks; then for four weeks the same dose was continued if possible. All drugs which the patient had been taking previously were continued throughout. All patients knew they were being given L-dopa and understood that different remedies were being used of which one might be more effective. They also knew that side effects and complications might ensue, but all willingly agreed to collaborate. The patients and the "blind" observer (R.C.H.) did not know which patient was receiving active remedy and which placebo at each stage.

Clinical Evaluation

Each patient was assessed clinically before each 10-week period and fortnightly thereafter by one of us (R.C.H.). Bradykinesia, rigidity (neck and limb), tremor, gait (with special reference to festination, retropulsion, shuffling, and associated movements), speech, handwriting, salivation, posture, facial masking, the glabellar tap sign and blepharoclonus were all assessed. Specific timed tests included walking a set distance, performing repeated hand grasps, rising from a standard chair, and restacking six books. Each timed test was performed thrice and the least time taken for the test was held to represent the patient's best performance at each attendance. The opinions of the patient and of relatives concerning everyday function and activity were also recorded.

A note of side effects—for example, involuntary movements, gastrointestinal symptoms, postural hypotension, cardiac arrhythmias, and psychic symptoms—was made at each attendance by one of us (J.G.P.) and the drug dosage was adjusted when necessary. The urine was analysed for protein, sugar, and acetone, and haemoglobin, white blood cells, platelets, blood urea, serum aspartate and alanine aminotransferase, alkaline phosphatase, and bilirubin were estimated fortnightly.

The patient's ability to perform everyday tasks was assessed independently by two occupational therapists in the kitchen and bathroom of the hospital department before each treatment period and at 6 and 10 weeks. Mood was also assessed with the Hildreth self-rating scale at each 0 and 10-week stage.

Method of Clinical Scoring.—Clinical features and timed tests were scored according to increasing disability. Thus rigidity and tremor were scored on a 0-4 scale on each side and scores for the two sides were added, giving a maximum of 8. Bradykinesia and gait were each scored 0-4, but the score was doubled to give these signs comparable "weighting." The other features and timed tests were scored 0-4 except for salivation (1 if excessive, 0 if normal) and for handwriting which was scored 0-2. Posture, facial masking, the glabellar tap sign, and blepharoclonus were not scored, but changes in these were noted.

The maximum disability score was thus 55; the patients

completing the trial had total scores between 14 and 39 before treatment. A score of 30 or more indicated severe disability (nine patients), 20-29 moderate disability (17 patients), and below 20 mild disability (five patients). Those with the three degrees of disability were evenly distributed in the three clinical groups (non-surgical and unilateral and bilateral thalamotomy). In assessing the effect of treatment the 10-week score after L-dopa was compared with the pretrial score and the change expressed as a percentage improvement. An improvement of 70% or more was regarded as marked, 30-70% as moderate, and 0-30% as mild or insignificant.

Results

Of 34 patients entering the trial two receiving L-dopa were withdrawn in the first four weeks owing to disabling postural hypotension in one and severe vomiting in the other. A further two patients did not complete the trial but sufficient data were available in these cases for consideration in the final analysis. One had shown definite improvement and minor side-effects only (involuntary movements), when she became unable to walk, complained of pain, and was found to have a fractured femoral neck. The other became hypotensive and ataxic on treatment with L-dopa and continued to deteriorate during placebo treatment; he was admitted to hospital and found to be suffering from multiple system degeneration (the Shy-Drager syndrome); he was therefore withdrawn from the trial.

L-Dopa Dosage.—The optimal dose (defined as that producing maximal improvement with tolerable side effects) ranged from 0.5 to 6 g daily, with an average of 3.1 g. Marked improvement was seen at all levels of dosage. The average dose ultimately attained was 3.1 g daily for each group—namely, non-surgical and unilateral and bilateral thalamotomy. There was a relationship between body weight and dosage achieved; the average daily dose for patients weighing 60 kg or more was 3.5 g compared with 2 g daily for those of less than 60 kg. The average optimum dose for the 18 men was 3.6 g against 2.5 g for the 14 women. This sex difference is probably explicable on a weight basis. The dosage of L-dopa attained bore no relationship to the dose of anticholinergic drugs which were being administered concurrently. A second trial now in progress has been designed to show whether such remedies modified the clinical response or determined the optimal dosage of L-dopa. The dosage of L-dopa which patients tolerated tended to decrease with time without any loss of clinical response.

RESPONSE TO TREATMENT

The results in 32 patients were analysed, but one was treated for only eight weeks. The pretreatment scores of the surgical and non-surgical groups were compared for each clinical feature and did not differ significantly. The response to treatment was also similar in each of the three groups (non-surgical and unilateral and bilateral operations). Only one measurement—namely, restacking of books—showed any significant difference; while on L-dopa the "unilateral thalamotomy" group improved significantly more than the "bilateral thalamotomy" group, $P < 0.02$. Data from the three groups were combined to give a final assessment of the response to treatment.

The change in total disability score from pretreatment to each two-weekly assessment was the measure of improvement obtained with the drug, and similarly with placebo. Group improvement was the average of the individual changes. Patients receiving L-dopa showed a highly significant average improvement at the end of each period (Table I). A definite placebo effect was noted until the 10th week (Table II), when the average improvement dropped to 2.1, which is sig-

nificant at the 5% level. Comparative improvements noted while on L-dopa and placebo are given in Table III; the superiority of the drug, already apparent at two weeks, is clear from four weeks onwards.

Of the 31 patients assessed after 10 weeks on L-dopa, 30 improved, 12 markedly (more than 70% improvement), 15 moderately (between 30 and 70% improvement), three mildly (up to 30%), and only one deteriorated slightly. Twenty-nine patients were assessed after 10 weeks on placebo. Four improved moderately, 13 mildly, one was the same, two showed moderate deterioration, and nine mild deterioration. A graphical comparison of the relative improvement in the clinical features assessed produced by L-dopa and placebo is given in Fig. 1.

The changes noted from pretreatment to 6 and 10 weeks in each 10-week period regardless of treatment are shown in Table IV. The average pretreatment score before the second 10-week period was much lower than that obtained before the first period. This was due to the "carry-over" effect, despite the four-week gap, of L-dopa in those patients who had it in the first period. By 6 and 10 weeks in the second period the effect of both L-dopa and placebo had stabilized (Table IV). Thus sudden withdrawal of L-dopa was not followed by any untoward effects.

Bradykinesia.—A highly significant average improvement from pretreatment to each two-weekly interval was seen with L-dopa. Lesser improvements were seen with placebo, and by 6, 8, and 10 weeks the superiority of L-dopa was highly significant (Table V).

Rigidity.—Rigidity also showed a highly significant improvement with L-dopa from four weeks onwards. No significant placebo effect was observed, and after 10 weeks on placebo patients had on average worsened slightly (Table VI). We conclude that though bradykinesia may be improved by encouragement and practice, rigidity is seldom thus influenced.

Tremor. Improvement in tremor was immediately apparent at two weeks, and by six weeks it was significant at the

FIG. 1—Percentage improvement in disability function from pretreatment to 10 weeks.

TABLE I—Mean Scores of Combined Clinical Features Before L-dopa Treatment and at 2-weekly Intervals, and Mean Improvements

	No. of Patients	Mean Score	Mean Improvement	S.E. of Difference	P
Pretreatment .. 2 weeks .. }	28	{ 24.1 17.9 }	6.2	0.96	<0.001
Pretreatment .. 4 weeks .. }	32	{ 22.7 11.3 }	11.4	1.13	<0.001
Pretreatment .. 6 weeks .. }	31	{ 22.8 10.4 }	12.4	1.18	<0.001
Pretreatment .. 8 weeks .. }	25	{ 24.0 8.8 }	15.2	1.40	<0.001
Pretreatment .. 10 weeks .. }	31	{ 22.8 8.8 }	14.0	1.48	<0.001

TABLE II—Mean Scores of Combined Clinical Features Before Placebo and at 2-Weekly Intervals, and Mean Improvements

	No. of Patients	Mean Score	Mean Improvement	S.E. of Difference	P
Pretreatment .. 2 weeks .. }	29	{ 23.6 21.1 }	2.5	0.835	<0.01
Pretreatment .. 4 weeks .. }	31	{ 23.3 19.4 }	3.9	0.893	<0.001
Pretreatment .. 6 weeks .. }	31	{ 23.3 19.4 }	3.9	0.934	<0.001
Pretreatment .. 8 weeks .. }	25	{ 24.2 19.7 }	4.5	1.06	<0.001
Pretreatment .. 10 weeks .. }	29	{ 23.4 21.3 }	2.1	1.02	<0.05

TABLE III—Comparisons between Improvements in Disability Scores of Patients while Receiving L-dopa and Placebo

	No. of Patients	Mean Improvement	Difference between Mean Improvements	S.E. of Difference	P
2 weeks { L-dopa .. Placebo .. }	28 29	{ 6.2 2.5 }	+ 3.7	1.273	<0.01
4 weeks { L-dopa .. Placebo .. }	32 31	{ 11.4 3.9 }	+ 7.5	1.445	<0.001
6 weeks { L-dopa .. Placebo .. }	31 31	{ 12.4 3.9 }	+ 8.5	1.508	<0.001
8 weeks { L-dopa .. Placebo .. }	25 25	{ 15.2 4.5 }	+ 10.7	1.749	<0.001
10 weeks { L-dopa .. Placebo .. }	31 29	{ 14.0 2.1 }	+ 11.9	1.822	<0.001

TABLE IV—Comparison of Total Disability Scores in First and Second Periods of Treatment whether on L-dopa or Placebo

	No. of Patients	Mean Score	Mean Improvement	S.E. of Difference	P
1st period { Pretreatment 6 weeks }	32	{ 26.2 14.8 }	11.4	1.189	<0.001
2nd period { Pretreatment 6 weeks }	30	{ 19.7 15.0 }	4.7	1.14	<0.001
1st period { Pretreatment 10 weeks }	32	{ 26.2 15.4 }	10.8	1.539	<0.001
2nd period { Pretreatment 10 weeks }	29	{ 19.6 14.4 }	5.2	1.557	<0.01

TABLE V—Effect of L-dopa and Placebo on Bradykinesia and Difference between Effects

	Weeks				
	2	4	6	8	10
Mean improvement from pre-treatment—L-dopa ..	1.0	1.9	2.6	3.1	3.1
Standard error of change ..	0.221	0.262	0.269	0.294	0.249
P ..	<0.001	<0.001	<0.001	<0.001	<0.001
Mean improvement from pre-treatment—Placebo ..	0.8	0.6	0.5	1.1	0.7
Standard error of change ..	0.243	0.257	0.258	0.325	0.277
P ..	<0.01	<0.05	>0.05*	<0.01	<0.02
Difference between L-dopa and Placebo ..	+0.2	+1.3	+2.1	+1.9	+2.4
Standard error of difference ..	0.327	0.367	0.373	0.439	0.371
P ..	>0.4	<0.01	<0.001	<0.001	<0.001

*Not significant.

TABLE VI—Effect of L-dopa and Placebo on Rigidity and Difference between Effects

	Weeks				
	2	4	6	8	10
Mean improvement from pre-treatment—L-dopa ..	0.79	1.95	1.75	2.32	2.29
Standard error of change ..	0.216	0.186	0.182	0.180	0.229
P ..	<0.01	<0.001	<0.001	<0.001	<0.001
Mean improvement from pre-treatment—Placebo ..	0.02	0.06	0.24	0.06	-0.31
Standard error of change ..	0.144	0.152	0.172	0.134	0.164
P ..	>0.9*	>0.6*	>0.1*	>0.6*	>0.5*
Difference between L-dopa and Placebo ..	0.77	1.89	1.51	2.26	2.60
Standard error of difference ..	0.257	0.241	0.251	0.223	0.285
P ..	<0.01	<0.001	<0.001	<0.001	<0.001

*Not significant.

TABLE VII—Effect of L-dopa and Placebo on Tremor and Difference between Effects

	Weeks				
	2	4	6	8	10
Mean improvement from pre-treatment—L-dopa ..	0.32	0.52	0.68	0.61	0.47
Standard error of change ..	0.129	0.156	0.180	0.236	0.162
P ..	<0.02	<0.01	<0.001	<0.02	<0.01
Mean improvement from pre-treatment—Placebo ..	-0.31	0.08	-0.05	-0.20	-0.14
Standard error of change ..	0.167	0.154	0.144	0.157	0.185
P ..	>0.05*	>0.6*	>0.7*	>0.2*	>0.4*
Difference between L-dopa and Placebo ..	+0.63	+0.44	+0.73	+0.81	+0.61
Standard error of difference ..	0.212	0.219	0.230	0.283	0.060
P ..	<0.01	>0.05*	<0.01	<0.01	<0.001

*Not significant.

TABLE VIII—Effect of L-dopa and Placebo on Gait and Difference between Effects

	Weeks				
	2	4	6	8	10
Mean improvement from pre-treatment—L-dopa ..	1.9	2.8	3.1	3.2	3.1
Standard error of change ..	0.313	0.385	0.361	0.492	0.486
P ..	<0.001	<0.001	<0.001	<0.001	<0.001
Mean improvement from pre-treatment—Placebo ..	1.3	1.7	1.6	1.1	0.4
Standard error of change ..	0.405	0.395	0.422	0.446	0.437
P ..	<0.01	<0.001	<0.001	<0.02	>0.3*
Difference between L-dopa and Placebo ..	+0.6	+1.2	+1.5	+2.0	+2.7
Standard error of difference ..	0.514	0.551	0.555	0.664	0.656
P ..	>0.2*	<0.05	<0.01	<0.01	<0.001

*Not significant.

0.1% level; at 10 weeks improvement was still significant, but only at the 1% level. Insignificant worsening occurred during the placebo period. The superiority of L-dopa over placebo (Table VII) was significant at all intervals except four weeks, and highly significant at 10 weeks. Though tremor is a variable phenomenon, a constant average improvement was noted at 2, 4, 6, 8, and 10 weeks during L-dopa treatment, while deterioration was observed at four out of the five intervals while on placebo.

Gait.—Improvement in gait was, on average, apparent at two weeks and continued to six weeks; from then until 10 weeks improvement was maintained and was highly significant. Some improvement occurred during the placebo period, but this effect was diminishing at eight weeks, and by 10 weeks had disappeared (Table VIII). The superiority of L-dopa over placebo was evident from four weeks onwards.

Handwriting.—No significant association emerged between L-dopa treatment and improved writing at 6 or 10 weeks, but when improvement did occur it was often dramatic (Fig. 2).

Speech.—An improvement in volume and modulation of speech with L-dopa was observed at both 6 and 10 weeks, $P<0.05$.

Salivation.—During L-dopa treatment all 6 of the 32 patients who had hypersalivation lost this symptom, while on placebo there was no change, $P<0.05$. Excessive dryness of the mouth was produced by L-dopa in 15 patients; thus 21 patients noted less salivary secretion during treatment. Sev-

Florence Goughley Pre-L-Dopa
Florence Goughley 6/52 L-Dopa
Florence Goughley 8/52 L-Dopa
J. E. Goughley 15 Albany Park Rd. 10/52 Off L-Dopa

FIG. 2—Handwriting of one patient, showing correction of frank micrographia with return of this feature on cessation of L-dopa.

eral noted a perversion of taste; food either lost its taste or had a burnt or "rubbery" flavour.

Timed Tests

The timed tests were selected in order to reflect changes in bradykinesia and rigidity as a check on clinical assessments. All showed a significant improvement on L-dopa, and often this was striking—for example, one man who required more than two minutes to walk 14 yards (13 m) could cover the distance in 7.8 seconds after 10 weeks of treatment.

Hand-grip.—The average improvement during L-dopa treatment was highly significant at 6 and 10 weeks. Despite a small average improvement at 6 and 10 weeks on placebo, L-dopa was superior, $P<0.01$.

Rising from a chair.—There was a significant improvement in performance at both 6 and 10 weeks on L-dopa and on placebo at 6 weeks, but at 10 weeks the placebo effect was lost and L-dopa was superior, $P<0.02$.

Walking a Set Distance.—With L-dopa there was a significant improvement at both 6 and 10 weeks. At six weeks the placebo also gave a significant improvement, but this was lost at 10 weeks when L-dopa was significantly better, $P<0.05$.

Restacking of Books.—Performance on L-dopa improved highly significantly at 6 and 10 weeks, $P<0.001$. Improvement was also shown at 6 and 10 weeks on placebo, $P<0.05$, but the patients did significantly better on L-dopa. As previously mentioned, the test results were significantly better in non-surgical cases and in those who had had a unilateral thalamotomy than in those who had had bilateral operations. The ability to restack books requires bimanual skills; it is possible that minimal corticospinal tract dysfunction consequent on multiple operations could be a factor responsible for the different degrees of improvement in this test seen in the "unilateral surgical" and "bilateral surgical" cases.

Clinical Features not Scored

The following clinical features were assessed qualitatively but were not "scored."

Posture and Facial Masking.—A stoop—severe, moderate or slight—was found in 28 patients; 23 showed detectable improvement on L-dopa but no change on placebo. A within-patient comparison showed this change to be significant at the 5% level. Facial masking, present in 31 patients, was improved in 21, particularly when initially it had been pronounced.

Glabellar Tap Sign.—The glabellar tap sign was positive in 27 patients and became negative on L-dopa in 13 (48%). As

noted by Klawans and Goodwin (1969), this occurred only in patients showing a good overall clinical response.

Blepharoclonus.—Blepharoclonus (rhythmical contractions of the closed eyelids) was seen in 19 cases and disappeared in 10 while on L-dopa. The frequency of contraction in our cases was similar to that of limb tremor.

Assessments of Functional Capacity

Functional disability as assessed by the two occupational therapists showed an improvement with L-dopa comparable to that found in the clinical "scores" in patients with marked or moderate disability. As mildly disabled patients performed well initially, their subsequent improvement was not reflected in this assessment.

Subjective impressions

Patients' Own Assessment.—The first response to L-dopa noted by the patients was variable. Some noticed improvement in wellbeing or mobility within two to three days—that is, on 0.5 g of L-dopa daily, while others noted no change until they had been treated for three to four weeks—that is, when receiving 3–4 g daily. There was no obvious reason for this variability, and the degree of eventual improvement obtained was not related to its time of onset. Most patients felt that they had improved during both the L-dopa and placebo periods; while at six weeks L-dopa was not better than placebo, $P < 0.5$, by 10 weeks it was highly significantly superior, $P < 0.001$.

Relatives' Assessment of Patients' Condition.—The subjective impression of relatives closely followed the patients' own assessments. At six weeks there was no significant difference between L-dopa and placebo, but at 10 weeks L-dopa was superior, $P < 0.01$. If the emergence of side effects had not coloured for the worse the patients' and relatives' impressions, we feel that the efficacy of L-dopa would have been reflected much earlier.

Mood

During the 10 weeks on L-dopa the average score on the Hildreth self-rating scale had changed from 41.4 to 46.5—a significant difference, $P < 0.01$. During the period on placebo no change was observed and the effect of the drug compared with placebo was significant, $P < 0.01$.

"Decoding"

Some degree of clinical "decoding" often occurred in that the "blind" observer was usually aware eventually which patients were receiving L-dopa. This usually resulted from the appearance of involuntary movements which (see below) developed in 75% of patients from two to nine weeks after starting treatment. We are satisfied that this "decoding" did not occur early enough to invalidate the results of the trial.

Side Effects

GASTROINTESTINAL SYMPTOMS

Seventy per cent. of patients suffered gastrointestinal side effects (nausea, vomiting, or anorexia) during L-dopa administration, though capsules were taken after meals. Usually they were transient but occasionally dose-limiting. The drug was stopped because of vomiting in one patient only. The symptoms usually followed the taking of capsules,

most often after the morning dose. Though in a few patients nausea was constant throughout the day, most patients felt well between doses and ate well. A few lost weight, probably due partly to the side effects and partly to the increased activity permitted by L-dopa.

HYPOTENSION

Twenty-five per cent. of patients had symptomatic hypotension (dizziness on standing up) while on L-dopa; one third of these were moderately or severely disabled, but no patient fainted. The drug was discontinued in one patient only because of severe, persistent hypotension. Our figure of 25% corresponds to the 23% reported by Yahr *et al.* (1969), but is considerably higher than in the series of Mawdsley (1970) and Cotzias (1969), who noted 6% and 4% respectively. Six of the eight patients with symptomatic postural hypotension were moderately hypertensive before treatment (diastolic B.P. consistently > 100 mm Hg). A further 25% of patients had asymptomatic hypotension (a fall of 30–60 mm Hg in systolic and 20–40 mm Hg in diastolic B.P.), and only three of these had previously been hypertensive. Demonstrable hypotension persisted throughout the treatment period in about half the patients.

CARDIAC COMPLICATIONS

No significant cardiac arrhythmias were noted in any of our patients, though a few complained of mild palpitations.

INVOLUNTARY MOVEMENTS

Seventy-five per cent. of patients had drug-induced involuntary movements at some stage. This is a higher incidence than that found by most other workers; Mawdsley (1970) found 33%, and Yahr *et al.* (1969) 62%. The full range of movements previously recorded was seen, and varied from mild tongue protrusions and foot-paddling movements to severe facial dyskinesias, gross rotatory head movements, severe athetoid limb movements, and painful dystonias (Table IX). All were dose-dependent and were improved by a reduction in dosage. The movements were not limited to those taking the highest doses of L-dopa and, as in other series, there were some whose movements increased while on a constant dosage.

The movements were either intermittent or constant and occasionally interrupted sleep. Half of the patients in whom they were intermittent noted that they occurred one to two hours after the last dose. Of the 24 patients thus affected 12 were non-surgical and 12 had had thalamotomies, three of the latter being bilateral and nine unilateral. All nine patients who had had unilateral operations developed dyskinesias. Only one of these developed limb movements on the side contralateral to the thalamotomy; in seven of the other eight they occurred only on the ipsilateral side. Three of the eight patients who had had bilateral operations developed movements; in two the onset was late and they remained axial, never involving the limbs; two of these three patients had

TABLE IX—Incidence and Types of Involuntary Movement Seen during L-dopa Treatment

Patients receiving L-dopa	32
Patients developing involuntary movements	24
Types of Involuntary Movement:	
Facial dyskinesias	19
Choreoathetoid (limb) movements	15
Head movement (rotatory or nodding)	11
Dystonic movements (2 spasmodic torticollis)	4
Trunk flexion/extension	4
Ballistic movements	2

had more than one operation on one or other side. Bilateral involuntary movements were seen in five patients, four of whom were non-surgical while one had had bilateral operations. There was a suggestion that the involuntary movements were sometimes more severe on the side of the body more severely affected by Parkinsonism.

Patients willingly tolerated obvious and disfiguring movements; almost all preferred the movements to their disability before treatment, and some even claimed to be unaware of them. No patient complained that movements interfered with eating or respiration as noted by Yahr *et al.* (1969). Speech was obviously affected by severe facial and oral dyskinesia in one patient, and in several patients walking was disturbed by athetoid or ballistic movements of the legs, which were severe enough in one to throw her to the ground. A few complained of painful dystonia affecting the neck, shoulder, upper arm, and trunk. One patient received L-dopa first and showed mild involuntary movements when on high dosage; these abated on placebo, but when the active drug was reintroduced he soon developed severe upper-limb dyskinesia, which disappeared as the dose was increased. This was the only case in which movements diminished with increasing L-dopa dosage.

No patient had to stop the drug because of movements, but six were particularly sensitive to this effect of L-dopa and developed severe, disabling, and dose-limiting movements on 1.5 g of L-dopa daily or less. In at least one of these the onset of involuntary movements prevented a satisfactory therapeutic response. Of these six "sensitive" patients (three men and three women), three had had unilateral surgery, one had had bilateral surgery, and two were non-surgical; all were normotensive, their ages ranged from 42 to 64 years and their disease duration from 8 to 27 years; three had severe Parkinsonism and three were mildly to moderately affected. Thus "sensitivity" could not be predicted by clinical criteria. In a few patients who received L-dopa during the first 10 weeks of the trial reintroduction of the drug at the end of the trial—that is, after another 14 weeks—resulted in the earlier emergence of involuntary movements. Hence despite the minor clinical "carry-over" effect there may be a prolonged retention of dopamine or of its metabolites in the relevant diencephalic areas.

ALTERED MENTAL STATE

Four patients had hallucinations during treatment and seven, including these four, were noted to be episodically confused. About 20% of patients, however, have confusional episodes on anticholinergic drugs alone (Duvoisin, 1969). Three patients became hypomanic; one was particularly sensitive, and after one capsule became uncontrollably hyperactive for about four hours. He was also taking dexamphetamine; but another patient who was also receiving this drug was not similarly affected. There was no significant alteration in sleep pattern; four patients slept better while receiving the drug and six complained of insomnia, due in two of them to involuntary movements. Two patients noted only a slight short-lived increase in libido.

SPEECH DETERIORATION

In seven patients, three of whom had had bilateral thalamotomy, increased dysarthria was noted. In four slurring had been present before treatment but in three it arose de novo. In one only did it seem that oral dyskinesia was the cause.

OTHER SIDE EFFECTS

In addition to three patients who complained of weight loss, some noted that their dentures became loose-fitting. One

patient noted limpness (hypotonia) of the limbs (he felt like "a rubber man").

LABORATORY FINDINGS

No significant alteration was noted in haemoglobin, white cell count, platelets, or blood urea, and the urine analysis remained normal. The serum aspartate aminotransferase and alkaline phosphatase occasionally rose, but only on four occasions to above normal; these rises were merely temporary despite continuation of the drug. Godwin-Austen *et al.* (1969) noted a rise of serum aspartate aminotransferase in two patients and of alkaline phosphatase in one, while Yahr *et al.* (1969) noted similar increases in seven patients and in one respectively.

Discussion

Though the period of L-dopa treatment in this trial was short (10 weeks) the results show that previous ventrolateral thalamotomy, whether unilateral or bilateral, produces no apparent modification in the time course or extent of the response when the results in such cases are compared with those obtained in a similar group of non-surgical patients. The average optimal daily dose was 3.1 g for each of the non-surgical and unilateral and bilateral thalamotomy groups. The average improvement in total disability score in "surgical" patients was 60%, as compared with 54% in those who had had no operation. These findings are contrary to those of Stellar *et al.* (1970), who compared 60 surgical and 30 non-surgical patients during treatment over one to nine months and concluded that surgical patients fared worse.

Our results, however, confirm the suggestion of Schwab (1969) that previous thalamotomy, though not reducing the incidence of dyskinesias, may afford some protection against drug-induced involuntary movements in the contralateral limbs, since though eight out of nine patients who had had unilateral operations developed such movements, in seven these were seen only on the side ipsilateral to the operation. It could be argued that this was because movements occurred on the side least affected by Parkinsonism. In non-surgical patients, however, the movements occurred bilaterally (in four patients) despite predominant affection of one or other side, or else were more striking on the more severely affected side. Furthermore, in seven patients who had had bilateral operations and who completed the trial, limb movements were seen in only one and were bilateral, while three patients experienced facial dyskinesias or head movements. If this operative "protection" is confirmed, then a possible explanation is that ventrolateral thalamotomy interrupts the pathway responsible for L-dopa-induced limb dyskinesia.

Involuntary movements, which occurred in 75% of the patients who completed the treatment period, were virtually limited to those who derived benefit and were most severe in those who improved most. In one case at least they did, however, limit the potential therapeutic effect. These movements may be due to the action of dopamine on catecholamine receptors, either striatal or extrastriatal, which are sensitized by lesions in the substantia nigra (Barbeau, 1970), as they are not seen in normal adults given the drug.

The degree of improvement in major disabling features—namely, bradykinesia and rigidity—was as noted in previous reports, being 84% and 67% respectively from pretreatment to 10 weeks; if the trial had been extended the improvement might well have been greater still. Improvement in other features which are functions of bradykinesia and rigidity, notably speech and gait, was also considerable. The reduced salivary secretion while continuing anticholinergic drugs suggests that hypersalivation, a sign which has often responded

to anticholinergic drugs, is treatable with equal or greater efficiency by L-dopa alone.

In our series the patient's age, the severity and duration of the disease, and the time since the last operation did not influence the therapeutic response. One limiting factor in both the "surgical" and "non-surgical" groups of patients was hypertension. Pre-existing hypertension (diastolic B.P. >100 mm Hg but <110 mm Hg) was found in 100% of patients showing little or no response and in only 25% and 33% respectively of those showing a marked or moderate response to treatment. No other obvious cause of a poor response was found; the average daily dose of L-dopa attained by this poorly-responding group was 3.3 g which is similar to the average final dose in the whole series (3.1 g).

Controllable side effects were seen in almost all patients; a note of caution is sounded by the occurrence of femoral neck fractures in two women, one during the trial and one shortly afterwards when the drug was reintroduced. Both were post-menopausal and both had been severely restricted in their activities by akinesia and rigidity. Both showed considerably increased mobility, and perhaps this sudden bound in activity against a background of disuse and of postmenopausal osteoporosis was sufficient to overstress the femur; in one case there was no apparent trauma and in the other it was minimal.

This trial was conducted under the auspices of the Medical Research Council's Working Party on L-dopa. We are grateful to Dr. A. M. Duffus and to Roche Products Limited for supplying the L-dopa (Larodopa) and placebo capsules which were used in the trial. We also wish to thank Mr. J. Hankinson and Dr. J. B. Foster for allowing us to include in the trial patients who were

under their care, and we are grateful to Mrs. Brenda Welsh and Miss Gillian Lough for carrying out the occupational therapy assessments. Some of the early mood assessments with use of the Hildreth self-rating scale were performed by Dr. Andrew Rabavilas.

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Prolonged Exposure: a Rapid Treatment for Phobias

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British Medical Journal, 1971, **1**, 13-15

Summary

Ten adult patients with long-standing specific phobias were treated by prolonged continuous exposure to their phobic objects in fantasy and reality without avoidance. All patients were greatly helped by four to five hours' treatment in two or three sessions, and all improved more after practice than after imaginal sessions. The treatment method is more economical and efficient than other methods described so far.

Introduction

Systematic desensitization has often been shown to be of value in the treatment of phobias (Marks, 1969), but is usually more effective in specific phobias than in agoraphobia. A previous trial (Marks, Boulougouris, and Marset, 1971) showed that another technique, implosion (or flooding), was

more effective than desensitization in agoraphobia and equally effective with specific phobias. In a more recent study of flooding (Watson and Marks, 1971) the patients were helped less than in the earlier trial. Watson and Marks gave imaginal sessions only, whereas Marks *et al.* (1971) used practice as well as imaginal sessions; it appeared that additional treatment in practice increased the effectiveness of treatment in imagination. Previous experience also suggested that prolonged practice sessions might be more effective than shorter ones, particularly when they could be devoted continuously to overcoming avoidance of or escape from the phobic object or situation.

This paper describes a pilot study of prolonged exposure in practice in 10 patients with specific phobias; clinical and physiological variables were monitored throughout treatment. As these patients can usually be attached to a polygraph while in the phobic situation more easily than those with agoraphobia, only specific phobias were used in this preliminary project.

Patients

All the patients were sufficiently distressed and disabled by their phobic symptoms to have requested treatment from their general practitioner. All were adults, presenting on account of recent complications of phobias which had been

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