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Combined Antidepressant Therapy

By FRANK WINSTON

It is still generally believed that it is dangerous to combine the tricyclic antidepressants with any of the M.A.O. inhibitors, and the Federal Drug Administration, the Witts Committee and the drug manufacturers caution against so doing. Several current texts reiterate these warnings. (Beck, 1967; Malitz, 1966: Shepherd *et al.*, 1968).

The reports of severe side effects which form the basis of these warnings were the subject of an editorial in the *Lancet* in 1965.

On the other hand, Sargant (1963), Beresford Davies (1963) and Gander (1965) have all reported on the treatment of large numbers of patients with various combinations of antidepressants without fatality or unusual side effects, and Pare (1965) and Dally (1967) have also advocated such treatment for patients with resistant depression.

Recent research into the aetiology of depression (*Lancet*, 1968) has made it possible for us to prescribe antidepressant medication hopefully directed at the biochemical 'lesion' involved. There is an increasing body of evidence that the ability to correct one's mood is dependent in some way on cerebral amine metabolism, the exact amines involved being at present the subject of some controversy, some investigators feeling that mood is related to the cerebral level of the catecholamines (Schildkraut, 1965) while others feel that it is related to the indoleamines (Dewhurst, 1968). The M.A.O. inhibitors act by preventing the destruction of the 'free' intracellular amines, and the tricyclic group of drugs prevent or slow down the uptake of these amines into the cell from their receptor sites. The fact that both these groups of drugs are antidepressant in effect is consistent with and tends to confirm the biogenic amine hypothesis. In view of the fact that these two groups of drugs have different modes of action it is not surprising that some patients react to one group and not to the other. There are, however, some patients who respond to neither of the two classes of antidepressants satisfactorily and either respond poorly to E.C.T. or consistently relapse. In which case, as Pare (1965) has pointed out, 'increasing the total amine concentration by giving an M.A.O. inhibitor and at the same time giving a member of the imipramine group of drugs can be expected to result in a greater antidepressant effect'. Pare warns that this will 'make the patient much more prone to hypertensive attacks'. However, the experience of Sargant and Gander suggests that this risk is not of a high order—certainly far less than the risk of suicide if the depression remains unrelieved.

I have been using antidepressant medications in combination in my practice for four years without encountering any side effects greater than when using the drugs separately; except that one patient on amitriptyline reported a pounding headache suggestive of a hypertensive episode one half hour after taking 5 mg. isocarboxazid, and the drug had to be stopped. Occasionally severe postural hypotension can be a problem, but it usually improves with reduction of the dose. However, it has been pointed out (Horwitz, 1968) that postural hypotension is an indicator of the therapeutic efficacy of antidepressant drugs. The most prominent side effect is weight gain. There is some evidence that the safest combination is isocarboxazid and amitriptyline (Pare, 1965; Dally, 1967), and when a patient is non-responsive to conventional treatment these are the two I generally use.

The patient is placed on amitriptyline up to 250 mg. daily. If there is no response amitriptyline is reduced to 100 mg. daily, and 5 mg. isocarboxazid daily is added. If there are no untoward side effects, such as unusual headache, the dose is increased to 10 mg. daily for seven days. Often at the end of that time the patient is rapidly improving, and it is seldom

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necessary to give more than 20 mg. isocarboxazid daily. There is extreme sensitivity to changes in dosage. One patient who was relapsing on 20 mg. isocarboxazid plus amitriptyline 25 mg. daily recovered and remained well when the dose was changed to 10 mg. isocarboxazid plus 50 mg. amitriptyline daily. She had been completely unresponsive to amitriptyline alone.

Four patients suffering from severe endogenous depression were placed on imipramine up to 250 mg. daily. Not responding satisfactorily, they were given E.C.T. The imipramine was discontinued and after a week tranylcypromine 30 mg. daily was started in the hope of preventing relapse. These patients still relapsed. On addition of 10–25 mg. amitriptyline daily they all started to improve again rapidly. One patient's symptoms completely resolved on 10 mg. daily (see history 2).

Results

The mean duration of illness was approximately 4 years (3 months—12 years). All patients who improved did so within a week or so of addition of the second drug. All had failed to maintain improvement with E.C.T., and 16 had been previously treated with at least one anti-depressant of each class and so acted to some extent as their own controls. For more convincing evidence of the value of the various combinations of antidepressants the reader is referred to Gander's (1967) series of 157 patients.

Case Histories

Case 1. M.B. a 32-year-old housewife was first seen in May 1964, sixteen months after the birth of her second child, with symptoms of depression, crying spells, fear of being alone or harming her children and suicidal ruminations. She had previously had a milder attack of depression at the age of 17 after an unhappy love affair. These symptoms had started the day after delivery. A diagnosis of post-puerperal depression was made and she was admitted to hospital for E.C.T. She received 14 E.C.T.'s but relapsed a week after discharge. She was placed on imipramine 200 mg. daily with transient improvement, but had to be admitted to hospital again two months later. Again she improved with E.C.T. but quickly relapsed. On 23 November, all symptoms had returned and she was replaced on imipramine 25 mg. t.i.d. Two days later she was symptom-free and remained so until her discharge on 30 November. The reason for the sudden improvement was not clear, but it was observed at the time that she had been placed on tranylcypromine 10 mg. b.i.d. on 20 October and this had inadvertently not been discontinued when she was placed on imipramine. Tranylcypromine was stopped and she was sent home on imipramine 25 mg. t.i.d. By 21 December she had begun to relapse; tranylcypromine 10 mg. b.i.d. was restarted in addition to the imipramine. Improvement was noted in a few weeks, and by 1 March 1965, she was feeling very well indeed and had put on 14 kg. in weight. She continued on imipramine and tranylcypromine until November 1965, but continued to take chlorpromazine 75 mg. b.i.d. which she had been taking since discharge from hospital. She was not seen again until 19 January, 1966, at which time she was 30 weeks pregnant. She was extremely depressed, with many obsessional ideas and thoughts of suicide. She was readmitted to hospital and replaced on imipramine and tranylcypromine; there was only very slight improvement after two weeks, and so she was given a further 11 E.C.T.'s at the end of which she was much better but not entirely symptom-free. Immediately after delivery her illness resolved completely. She was sent home on tranylcypromine 10 mg. b.i.d., imipramine 25 mg. t.i.d. and trifluoperazine 2 mg. t.i.d. on 14 March 1966. She has remained symptom-free since that time and has had two further pregnancies without any return of depression. She was still taking 10 mg. tranylcypromine and 10 mg. imipramine daily in October. 1969, as attempts to discontinue either drug completely always resulted in a recurrence of depression.

Case 2. P.K. a 24-year-old housewife was first seen in March, 1968. She had been seriously depressed for three months but had had a similar episode some two years previously when her husband went to Vietnam. She improved when he came back, but soon relapsed. She had severe depression with phobic features and a stiff neck. A diagnosis was made of mixed depressive reaction, and she was treated successively with imipramine, E.C.T., tranylcypromine, tryptophan and sedative insulin, together with supportive psychotherapy. She always improved initially in response to each new treatment, but relapsed within a few weeks. She improved on sedative insulin together with tranylcypromine 20 mg. daily, but shortly after leaving hospital began to relapse in spite of increase of medication to 30 mg. daily. On 10 December she was placed on amitriptyline 10 mg. daily and tranylcypromine was reduced to 20 mg. daily. By 16 December there was a marked improvement. On 3rd January, she appeared symptom-free except for some difficulty in sleeping. Amitriptyline was increased to 25 mg. daily. Three days later she began to show signs of hypomania and she herself cut her dosage back to 10 mg. On 14 January she was symptom-free. On 14 February she had got herself a job (for the whole of the previous year she had been afraid to leave her house alone or go for a car ride), but said she was a little nervous just in the mornings and put it down to anxiety about her job. It was then discovered she had discontinued her amitriptyline and had reduced tranylcypromine to 10 mg. daily. Tranylcypromine was increased to 10 mg. b.i.d

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TABLE I

Drug combination	No. of patients	Complete resolution	Considerable improvement	Some impr.	No impr.	C.R. + C.I.
Amitriptyline and isocarboxazid*	13	3	6	1	3	9 (69·2%)
Amitriptyline and tranylcypromine**	6	3	1	1	1	4 (66·6%)
Imipramine and Tranylcypromine	1	1				1 (100%)
Totals	20	7	7	2	4	14 (70%)

* Max. daily ratio 100/30 mg. Min. maint. 25/5 mg.
** Max. daily ratio 100/30 mg. Min. maint. 10/10 mg.

TABLE II

Showing number of hospital admissions and E.C.T.'s in year preceding and year following institution of combined therapy

	Yr. before		Yr. after			On comb.
	Hosp. adm.	E.C.T.	Hosp. adm.	E.C.T.	Date treatment started	Oct. '69
(a) Patients who improved						
M.B.	2	28	0	0	Dec. 64 see history	Yes
V.H.	2	4	0	6	May 66	Yes
B.K.	0	4	1	9	June 66 relapsed Oct. 66	No
R.V.	0	7	0	0	July 66	Yes
A.M.	2	15	0	0	Apr. 67	Yes
M.E.	5	8	0	0	Apr. 67	Yes
A.O.	0	0	0	0	June 67	Yes
R.J.	3	9	1	0	June 67 relapsed Oct. 67 (1)	No
M.T.	1	10	0	0	Oct. 67	Yes
M.R.	1	12	0	0	Nov. 67	Yes
R.B.	0	0	0	0	Oct. 68 d.c. Feb. 69 (2)	No
D.T.	1	9	0	0	Oct. 68	Yes
L.T.	1	7	0	0	Oct. 68	Yes
H.B.	2	7	0	0	Nov. 68 last seen Apr. 69	?
D.G.	2	16	0	0	Nov. 68 d.c. June 69	No
P.K.	1	9	0	0	Dec. 68 see history	?
mean for Grp. (a)	1·44	9·06	·125	·94		
(b) Patients unimproved						Discontinued after
D.F.	1	13	2	6	Mar. 67 (3)	4 weeks
J.E.	2	15	2	22	Jan. 68	7 weeks
N.P.	1	12	1	4	May 68	7 weeks
M.G.	0	0	1	6	Nov. 68	8 weeks
mean for Grp. (b)	1	10	1·5	9·5		

(1) Now maintained on lithium and isocarboxazid.
(2) Amitriptyline discontinued because of intestinal and bladder atony. She immediately became more depressed. Condition improved on addition of l-tryptophan.
(3) Improved on l-tryptophan.

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and amitriptyline 10 mg. daily restarted. By 18 April she was symptom-free. She left for England in June, 1969. In ten months before combined therapy she was seen 67 times. In six months following she was seen 6 times.

Discussion

Of the 20 patients treated 18 were women. The age range was 24–83 years. Nineteen were treated in the three year period 1966–68 during which time 273 new patients were seen. The group therefore comprised approximately 7 per cent. All patients who showed a good response to combined antidepressants also showed a good response to E.C.T. but relapsed quickly. When combined antidepressants were of benefit patients had shown at least a transient response to one of them. Sometimes it was necessary to give E.C.T. at the same time as combined therapy to induce remission. Combined antidepressants may be able to prevent relapse after E.C.T. but be unable to induce remission once the depression is well established (see Case 1).

The fact that most of the severe reactions reported in the literature have been the result of a massive overdose of the combined drugs, generally in suicidal attempts, or followed the parenteral administration of imipramine to a patient taking M.A.O. inhibitors (*Lancet*, 1965) suggests that they are directly related to dosage and speed of intake, careful control of which may well determine the difference between recovery and disaster. Therefore, in order to avoid too rapid an increase in catecholamine concentration, and to allow for individual patient sensitivity, the second antidepressant should be added in the minimum possible dose, increasing gradually by weekly increments until the desired response is achieved. At the time the second drug is added it is advisable to reduce the dose of the first. Neither drug should be given parenterally, and blood pressures should be checked frequently.

Summary

The benefits of the use of combined antidepressants are weighed against the potential hazards involved and an endeavour is made to show that, providing prudence and caution are employed, the M.A.O. inhibitors and the tricyclic antidepressants can be used together without dire results and with considerable benefit to many patients with chronic resistant depression.

Official name	*Brand name*
Amitriptyline	Tryptizol, Elavil
Imipramine	Tofranil
Tranylcypromine	Parnate
Isocarboxazid	Marplan
Trifluoperazine	Stelazine
Chlorpromazine	Largactil, Thorazine

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