AMITRIPTYLINE IN DEPRESSIVE STATES:
A CONTROLLED TRIAL

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SINCE its introduction in 1938, electroconvulsive therapy (E.C.T.) has shown itself to be a dramatically effective, unusually safe treatment for severe depressive states ("melancholias", "endogenous" or "psychotic" depressions). Nevertheless, it is repugnant to many patients and psychiatrists, produces a troublesome, if transient, amnesia—especially in older individuals—and is occasionally complicated by fractures and dislocations as well as by anaesthetic and relaxant misadventures. Worst of all, as early studies showed, of the 80–90 per cent. of severe depressives who respond to E.C.T., some 30 per cent. relapse (Huston and Locher, 1948 a, b). Recent work suggests that the rate of relapse may often be higher still—thus of 94 per cent. of a group of patients who had responded to E.C.T., Kiloh and Ball (1961) reported that 46 per cent. had relapsed during the six months following the cessation of treatment. For these reasons, the trend to chemotherapy initiated by the advent of effective antidepressant compounds in 1957 continues to develop, and signs are becoming manifest that within a few years E.C.T. may be replaced by pharmacotherapy.

The newer antidepressants, bringing into prominence the question of the type of patient that may be expected to respond to their administration, have reawakened interest in the classification and phenomenology of depressive conditions, perennial problems of psychiatric nosology (Lehmann, 1959; Roth, 1959). These issues first became therapeutically important when the efficacy of E.C.T. was discovered. Thus, psychiatrists might adhere to the endogenous-reactive dichotomy (Gillespie, 1926; Rogerson, 1940) or, finding such a qualitative distinction valueless (Mapother, 1926; Lewis, 1934), might prefer to classify depression quantitatively by severity, but when E.C.T. was introduced they were compelled to find ways to select the patients in whom a response might reasonably be expected. Today's antidepressant drugs point up the same problem; as in the case of E.C.T., also an empirically based remedy, they compel classification of depressions in terms of anticipated response to treatment.

The treatment of depressive conditions by drugs and other means has recently been reviewed by Rees (1960). In 1957 the amphetamines ("Dexedrine" "Methedrine"), all relatively weak antidepressants used mainly in out-patients, began to be replaced by the monoamine oxidase inhibitor iproniazid ("Marsilid") and the dibenzine derivative imipramine ("Tofranil"). Iproniazid and the newer less toxic M.A.O. inhibitors that were developed from it soon demonstrated that they were effective antidepressants, especially useful in the treatment of atypical and reactive depressions (Sargant, 1961). Imipramine, on the other hand, was found to be of value in the treatment of endogenous

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depressions as well as in milder "neurotic" or "reactive" cases. Controlled trials on in-patients and out-patients (Lehmann *et al.*, 1958; Ball and Kiloh 1959; Doust *et al.*, 1959; Holt *et al.*, 1960; Leyberg and Denmark, 1959; Sloane *et al.*, 1959; Ashby and Collins, 1961; Bruce *et al.*, 1960; Kenning *et al.*, 1960; Kiloh and Ball, 1961, Rees *et al.*, 1961; Rothman *et al.*, 1961) have shown conclusively that imipramine is an unusually effective chemotherapeutic agent for treating severe depressive states. Local experience in Victoria is in agreement with this finding (Stoller, 1960).

AMITRIPTYLINE

("Elavil" "Tryptizol" "Tryptanol")

This new antidepressant is not a monoamine oxidase inhibitor; chemically it is [5-(3-dimethylaminopropylidene)-dibenzo [a, d] [1, 4] cycloheptidiene hydrochloride]. It thus resembles both chlorpromazine and imipramine.

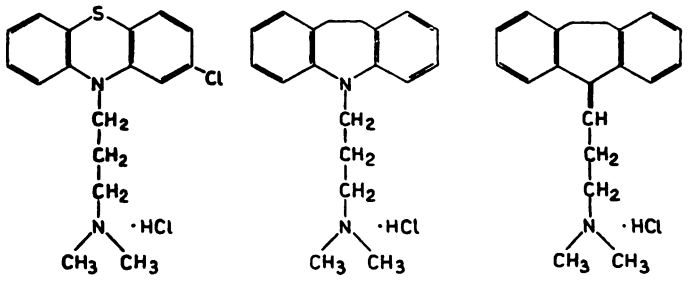


FIG. 1.

Amitriptyline's pharmacodynamic actions have been reviewed by Vernier (1961). Extensive experimentation in animals has shown that the compound exerts weak tranquillizing and disrupting effects on the EEG and operant behaviour; it is a fairly strong anti-convulsant, possessed of weak peripheral atropine-like actions, strong antihistaminic properties and weak antiserotonin effects. It produces a degree of adrenergic blockade and has a gastric antisecretory effect. It is rapidly metabolized in the body in a manner similar to imipramine.

In its effects on the human psychogalvanic reflex, amitriptyline occupies an intermediate position between chlorpromazine and imipramine (Alexander 1961). When administered to male patients suffering from neurotic depressions, amitriptyline beneficially affected mood and perception (Ostefeld, 1961).

Clinically, however it is administered, amitriptyline is stated to be a well-tolerated drug which acts in a manner reminiscent of both chlorpromazine and imipramine. Early clinical experience showed that depressions accompanied by high levels of anxiety in addition to psychomotor retardation respond particularly well to oral doses of 75–225 mg. daily; 50 mg. thrice daily was the usual level (Dorfman, 1960). Freed (1960) found that in severe cases of tension and anxiety, even in elderly patients with cerebral damage, amitriptyline in doses of 10–15 mg. could usefully be given intravenously without untoward effects. In involutional melancholia, amitriptyline has been stated to be the treatment of choice, although other types of depression have also responded (Ayd, 1960). More successfully than any other drug, it has been

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claimed, amitriptyline alleviates both anxiety and depression and bridges the divergent syndromes encountered in depressive illnesses (Dunlop, 1961). In the treatment of endogenous depression, amitriptyline has been stated to be the most effective pharmacological tool that we at present possess (von Arnold and Foitl, 1961). Protracted therapy is usually necessary to guard against relapse, and it is said that administration of the drug should be continued for at least three months after a beneficial therapeutic response is obtained (Ayd, 1961). In addition to the treatment of "pure" depressives, amitriptyline has been used with good results to alleviate the depression, anxiety and anergia that may accompany non-depressive psychoses, physical illnesses and dermatoses (Barsa and Saunders, 1961; Dorfman, 1961; Feldman, 1961; Pressman and Weiss, 1961; Vaisberg and Saunders, 1961; Zelcer, 1961).

From the work thus far published it would appear that amitriptyline has a number of significant advantages over earlier antidepressants. While more effective in the alleviation of depression than the amphetamines and methylphenidate, amitriptyline, it is asserted, does not produce tachycardia, insomnia or anorexia, the typical side-effects of these psychomotor stimulants. Since amitriptyline is a true antidepressant, it is claimed to be more effective in the treatment of depression accompanied by anxiety than chlorpromazine which, though it may alleviate anxiety, leaves depression untouched. As amitriptyline is not a monoamine oxidase inhibitor and has been shown to be unusually free from toxicity, it may reasonably be expected not to lead to the blood dyscrasias and hepatic complications that have occurred with M.A.O. inhibitors. Whilst at least as effective as imipramine in alleviating depression, it has been stated to possess the additional advantages of a rapidly evident "built-in" tranquillizing effect and relatively innocuous side-effects. Further, patients unresponsive to imipramine have been noticed to respond to amitriptyline and vice versa. If these claims are true, amitriptyline promises to be a useful drug indeed.

A Controlled Trial of Amitriptyline

Clearly, on the basis of published work, amitriptyline's biggest rival, especially in cases of endogenous depression, is imipramine. Controlled trials have already established that imipramine is a valuable form of treatment in both endogenous and reactive depressions, and one investigation (Kiloh and Ball, 1961) suggests that in these conditions, six months after either treatment has been given, imipramine is as effective as E.C.T. At the time of writing, since its efficacy has convincingly been established and its side-effects described in considerable detail, imipramine, as specific referent agent, is the most appropriate form of treatment with which to compare a new antidepressant such as amitriptyline. In the study to be described, therefore, since neither was considered necessary, the inclusion of placebo and E.C.T. groups was avoided. Instead, the efficacy of amitriptyline was investigated as part of a study planned for completion in three consecutive phases:

1. A double blind controlled trial of amitriptyline and imipramine in female patients hospitalized with depressive states.
2. Follow up of treated cases after 3 and 6 months.
3. An investigation of the phenomenology of the depressive states shown by female patients admitted to Royal Park Psychiatric Hospital, Melbourne, with a view to the subsequent isolation of specific criteria for the rational administration of anti-depressant drugs.

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As the first phase of the investigation has been completed, the findings on 73 patients are now presented.

Setting of the Study

Royal Park Psychiatric Hospital is an early treatment centre for acute psychiatric admissions which serves a metropolitan and rural population of approximately one million people. Situated within three miles of the centre of Melbourne, it is an open hospital with two closed admission wards—one for each sex. Of Royal Park's 240 patients, 140 are women; they are housed in villa type wards containing 35 or fewer beds, and are cared for by a staff of 14 physicians and 90 nurses. The Hospital is a major psychiatric teaching facility of the University of Melbourne.

Currently, about 1,700 women are admitted annually. Some two-thirds are treated in the unit, staying an average of one month; the remainder, with more adverse prognoses, are transferred to longer-stay hospitals. Admissions are virtually unselected and cover the whole spectrum of adult psychiatric disorder; approximately 25 per cent. of all female admissions present with depressive illnesses.

Experimental Hypotheses

Two null hypotheses were taken:

(*i*) Amitriptyline is no more efficacious than imipramine in the treatment of depressive states (as defined below) as judged by the results at one, four, and in some cases six, weeks after initiation of treatment with the two drugs.

(*ii*) Amitriptyline produces side-effects that are no less severe and troublesome than those produced by imipramine.

Methodology

(*i*) *Selection of patients.* Female patients were chosen because the great majority of cases of depressive illness admitted to Royal Park Psychiatric Hospital are women (Cade & Krupinski 1961). Those included in the trial were aged between 30 and 70, and able to remain in hospital at least four weeks; their previous treatment had not included E.C.T. in the previous three months or major antidepressant drugs (amitriptyline, imipramine or M.A.O. inhibitors) in the preceding two weeks. Their illnesses were not complicated by severe physical disabilities such as glaucoma, epilepsy or uncompensated cardiac, renal or hepatic disease; finally, when immigrants were included, they had no severe language barrier. Providing these initial criteria were satisfied, consecutive patients were taken into the study as long as the pattern of their illnesses revealed, as a primary manifestation, a persistent alteration of mood exceeding customary sadness, to the examiner, and constituting a major feature of the illness. This primary affective alteration had to be supported by one or more of the following features: self-depreciation, hypochondriasis, retardation or agitation. Depressions clearly secondary to other psychiatric illnesses such as schizophrenia, obsessional neurosis, dementia or severe oligophrenia, were excluded. Subsequently, in order to facilitate comparison with the work of other investigators, each patient was assigned either to the "endogenous" or "psychotic" variety of depression or to the "reactive" or "neurotic" form of the disorder.

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Potential subjects were chosen from daily screening interviews carried out on all admissions by one of the authors (C.G.B.). In most cases patients were observed for three days or more before being taken into the trial. This enabled information to be gathered to ensure that the criteria for selection were satisfied, as well as to facilitate the establishment of a firm diagnosis; in addition, through the three day delay, transient situational reactions could be excluded. Before entry to the trial, patients received full physical and psychiatric examinations, weight and blood pressure (recumbent and erect) were recorded and a number of laboratory tests were carried out, These included haematological examinations (Hb, WBC and ESR), serum bromide levels, the Kline reaction, liver function tests (alkaline phosphatase, cephalin flocculation) and urine analysis. Salient features of the psychiatric history were recorded on a specially constructed form; socio-economic background was assessed by a social worker on a form elaborated for the study.

(*ii*) *Organization and management of patients.* Selected patients were allocated to one physician (W.F.G.) and in the course of the trial naturally received a good deal of extra attention. Nevertheless to ensure that milieu influences were kept as constant as possible, only two wards were used in the study. After as short a period in the admission ward as their clinical condition permitted, patients were transferred to a 21 bed open convalescent villa taken over specifically for this purpose. As soon as practicable, patients were referred to occupational therapy; they worked in a standardized situation as a single group under the guidance of the same two occupational therapists.

(*iii*) *Allocation to groups: drug administration.* After initial evaluation on Hamilton's (1960) scale for quantifying depressive illnesses, patients were allocated to one of four groups delineated on the basis of two leading prognostic criteria, age and severity of illness. "Young mild" depressives were aged between 30 and 49 and, out of a possible maximum score of 100, had total scale scores below 40; "young severe" depressives were between 30 and 49 and had total scale scores above 40. Similar criteria of severity were used in the "old mild" and "old severe" groups, who were aged between 50 and 70. Each patient entering the appropriate group received a code number for use in drug administration. This method was chosen in order to avoid too great a degree of heterogeneity in the illnesses of patients undergoing the trial as well as to ensure, through the use of a factorial design, facilitation of the study of drug effects in relation to age and severity. The distribution of the 73 patients by groups is shown in Table I.

TABLE I

Patients Included in the Trial

Age/Severity	"Mild" Depressives (Scale Score 0–39)		"Severe" Depressives (Scale Score 40+)	
	Amitrip.	Imip.	Amitrip.	Imip.
Young (30–49)	2	2	12	12
Old (50–70)	5	5	18	17

The hospital pharmacist dispensed the appropriate drug in identical orange capsules, each containing 25 mg., according to a random numerical code which ensured equal distribution of the two drugs to patients in each group. Only the pharmacist and the investigator not involved in rating patients (N.F.H.) had access to this code. The nursing staff were fully apprised of the

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double blind nature of the study; they were asked to be more than usually careful in ensuring ingestion of medication and specifically requested to refrain from opening capsules before administration. All medication was administered orally and dosage was arbitrarily fixed at 150 mg. daily for the first week. 200 mg. were then given for the next three (or five) weeks. This was followed on discharge by a maintenance dose of 100 mg. daily.

After one month of in-patient treatment, patients considered to have improved sufficiently were discharged on maintenance dosage. Alternatively, if they were not appreciably better, they were given E.C.T. If a slight but significant improvement was judged to have occurred, patients were given a further two weeks in hospital on full dosage; at the end of this period the patient was either discharged on maintenance dosage or treatment was discontinued and E.C.T. was given. In 7 cases—either for socio-economic reasons (5) or where a need for a further gain in weight was apparent (2)—discharge was delayed beyond these arbitrary times, and the dosage was reduced to maintenance levels. Two patients who improved rapidly and were unwilling to remain in hospital were allowed home after two weeks on full dosage of the capsules; they returned to hospital as out-patients for their one month assessments.

Throughout the trial, with the exception of night sedation (sodium amylobarbitone 3–6 gr.), other medication was restricted to the very occasional use of intramuscular chlorpromazine.

Clinical Evaluation

Change in patients selected to participate in the trial was blindly evaluated in several ways:

1. *Rating Scale Scores.* Two independent ratings, later summed to make a total score, were made at a joint interview of each patient by two of the authors (C.G.B. and A.H.). The ratings were carried out initially, after one week and one month of treatment. Patients who stayed in the trial an extra fortnight received an additional rating at the end of this period. Hamilton's (1960) scale which quantifies 17 "target symptoms" of depression was used. The maximum possible scale score was $2 \times 50 = 100$.

2. *Overall Clinical Assessments.* These were made on the severity of the patients' illnesses at intervals corresponding to the Hamilton scale assessments by the two physicians who interviewed the patient to complete the rating scale. Depression was rated as 0=absent, 1=mild, 2=moderate, 3=severe or 4=extremely severe. Summing the scores of the two raters gave a possible maximum overall clinical assessment score of 8.

3. *Occupational Therapy Ratings.* Two independent ratings, later summed to make a total score, were made by two occupational therapists in a standardized occupational therapy situation at times corresponding as closely as possible to the times of the Hamilton scale assessments. An occupational therapy rating scale constructed for the investigation was used; it quantified 11 items of behaviour under (1) Task performance (grasp of instructions, attention to task, motivation and self-grading of own performance), (2) Symptoms (depression, retardation, agitation, physical complaints) and (3) Relationships (rapport with O.T., socialization, overall attitude to O.T.). The total scale score was 33; summing the two raters' scores gave a possible maximum score of 66.

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4. *Side-Effects Ratings.* These were made thrice weekly by one of the authors (W.F.G.) using a scale constructed to include the reported side-effects of amitriptyline and imipramine. Each symptom was quantified on 4 points of severity; patients and nursing staff were asked to bring possible side-effects to the rater's attention. Since it was considered extremely important to differentiate true side-effects from alleged "side-effects" constituting part of the patients' illnesses, initial pre-drug assessments were always made.

5. *Outcome of Treatment.* Finally the two drugs were compared as to whether patients were discharged "cured" (after 4 to 6 weeks) or alternatively had to go on to receive E.C.T.

RESULTS

Despite the frequency with which depressive states occur and the high percentage of hospital admissions they constitute, six months elapsed before 73 patients were collected who satisfied the study criteria. In this period 800 female patients were admitted to the unit, some 250 of whom presented with depressive disorders. Of the 180 who were rejected, the symptoms of 19 per cent. responded rapidly to the hospital environment; 21 per cent. had had recent major anti-depressive drug therapy; 15 per cent. were outside the age range and 13 per cent. had had recent E.C.T. In 15 per cent. depression was found to be "secondary" (principally to schizophrenic illness); 11 per cent. had too severe a language barrier to allow of valid ratings, and 6 per cent, were suffering from associated severe physical disorders.

As was to be expected from the method of allocation to the drugs, in socio-economic background there were no significant differences between the two groups; 85 per cent of the patients had been born in Australia. The mean age was 52·0, with a standard deviation of 10·85 years. Mean age of the "young" (under 50 years of age) group was 41·5 and that of the "old" group 58·6. 86 per cent. were or had been married, and these most commonly had had one, two or three children. Only 8 per cent. had gone beyond the primary school level, and vocational qualifications for the majority were restricted to semi-skilled industrial and clerical work. The majority were housewives, and all 15 per cent. who worked were employees. Precise figures about income were not obtained, but it is known that 11 per cent. depended on their own earnings, 45 per cent. on their husbands' earnings, and 35 per cent. on pensions. Dwellings were owned or being paid for by 62 per cent., the remainder living in rented houses or flats. The general picture was that of a predominantly lower-middle class socio-economic group, with an assured but usually low income and generally low levels of education, vocational training and experience.

In psychiatric background there were no significant differences between the two drug groups. Of the 73 patients included in the study, 46 per cent. had never previously been hospitalized for mental illness; 25 per cent. had been in hospital once before and 29 per cent. had been hospitalized two or more times. 62 per cent. of patients had first required medical attention for their mental condition within the last two years; 12 per cent. had needed help between 3 and 5 years preceding their current illnesses and 24 per cent. had had to get assistance between 6 and 20 years previously. 10 per cent. of the 73 patients had received some antidepressive therapy (within the specified limits) prior to admission; 6 patients had been given drugs, and one had had E.C.T. One patient had developed her illness within a week, but in the great

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majority (76 per cent.) the illness had taken one to eight weeks to develop; in 23 per cent. the illness had developed more insidiously. No precipitants could be found in 52 per cent. of patients; 33 per cent. had illnesses apparently precipitated by psychological stresses—either domestic anxieties such as grief, problems with children or in-laws, or more general stresses, such as anxiety following a car accident or in relation to impending surgery; physical precipitants such as alcohol, gynaecological conditions, the puerperium, hypertension, influenza, operation and the ingestion of reserpine were in evidence in the remaining 25 per cent.

During the trial no significant alteration in blood pressure or other somatic functions was noted and both drugs, as gauged by the various laboratory investigations performed, appeared safe and non-toxic in the doses that were used. One 65 year old patient died on the 20th day of imipramine administration; she developed a confusional state followed by generalized epileptiform activity and hyperpyrexia. Autopsy revealed that death had been due to pneumonia, and although the level of imipramine in the liver was unusually high, the pathologist's report stated that it was not possible to implicate imipramine directly in leading to the patient's decease.

The ease with which the selected patients, many of them severely depressed, were managed during the investigation was quite striking. Only one patient was rejected on the grounds of severity (and this essentially because of refusal of oral medication) and none of those accepted had to be given E.C.T. before the completion of 4 weeks of drug therapy. A few patients required occasional intramuscular chlorpromazine in the early stages of treatment, but this adjunct was used sparingly and only for extremely severe accesses of distress. This was all the more impressive as the great majority of the patients spent virtually their whole hospital period in the occupational therapy centre and in an adequately but not specially staffed open ward.

The Mann-Whitney U Test, corrected for ties (Siegel, 1956) was used to test the significance of differences found between the drug groups on physicians' ratings, overall clinical assessments and ratings by occupational therapists. The distributions of these various ratings were rarely normal in appearance, and "t" tests or other statistics based on the normal distribution or on interval scales would have been of dubious merit. All probabilities quoted are based on one-tailed tests, as the research hypotheses underlying the study specified the direction of the predicted differences between the two drugs.

It is convenient to consider the results of the investigation in terms of the methods employed to assess change in the selected patients. These comprised:

1. *Rating Scale Scores*

Table II shows the results of the trial in the total group of patients in terms of the ability of amitriptyline and imipramine to ameliorate the symptoms of depression itemized in Hamilton's scale.

It is evident that, at the end of one week, amitriptyline was generally, though slightly, superior to imipramine in improving the majority of the symptoms of depression. On two symptoms—delayed insomnia ($p = \cdot 01$) and middle insomnia ($p = \cdot 05$)—this superiority attained statistical significance. The total improvement score of the amitriptyline-treated group at the end of one week was slightly but not significantly higher than that of the imipramine group. After one month of treatment the superiority of amitriptyline was more clearly evident. It was significantly superior to imipramine in alleviating the following symptoms: gastrointestinal somatic symptoms ($p = \cdot 005$), delayed

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insomnia (p=·015), agitation (p=·04), initial insomnia (p=·05) and genital symptoms (p=·05). The total improvement score obtained with amitriptyline was appreciably greater than that produced by imipramine. The difference was almost significant at the 1 per cent. level.

TABLE II

Mean Improvement Scores on Physicians' Scale Ratings of Total Group

Specific Depressive Symptom	Possible Range of Scores	After 1 Week Amitrip. n=37	After 1 Week Imip. n=36	After 4 Weeks Amitrip. n=37	After 4 Weeks Imip. n=36
Depressed Mood	0–8	1·4	1·2	3·2	2·4
Retardation	0–8	·7	·7	2·0	1·7
Works & Interests	0–8	1·9	1·8	3·6	2·9
Guilt	0–8	·8	·8	2·1	1·5
Suicide	0–8	2·1	2·1	2·9	2·5
Psychic Anxiety	0–8	1·6	1·6	2·8	2·4
Somatic Anxiety	0–8	1·8	1·1	1·9	2·0
Hypochondriasis	0–8	·7	1·0	1·4	1·1
Agitation	0–4	1·2	1·2	1·7*	1·2
Initial Insomnia	0–4	1·1	·8	2·2*	1·7
Middle Insomnia	0–4	·7*	−·1	1·3	·8
Delayed Insomnia	0–4	·9†	−·3	1·6*	·7
Somatic Symptoms (Gastro-Int.)	0–4	1·2	·9	2·4†	1·5
Somatic Symptoms (General)	0–4	·8	1·0	1·8	1·5
Genital Symptoms	0–4	·9	·7	1·6*	·9
Loss of Weight	0–4	·0	·0	1·9	1·6
Loss of Insight	0–4	·3	·1	·7	·3
Total Improvement Score	0–100	17·9	14·7	35·2*	26·7

* Significant at 5 per cent. level.
† Significant at 1 per cent. level.

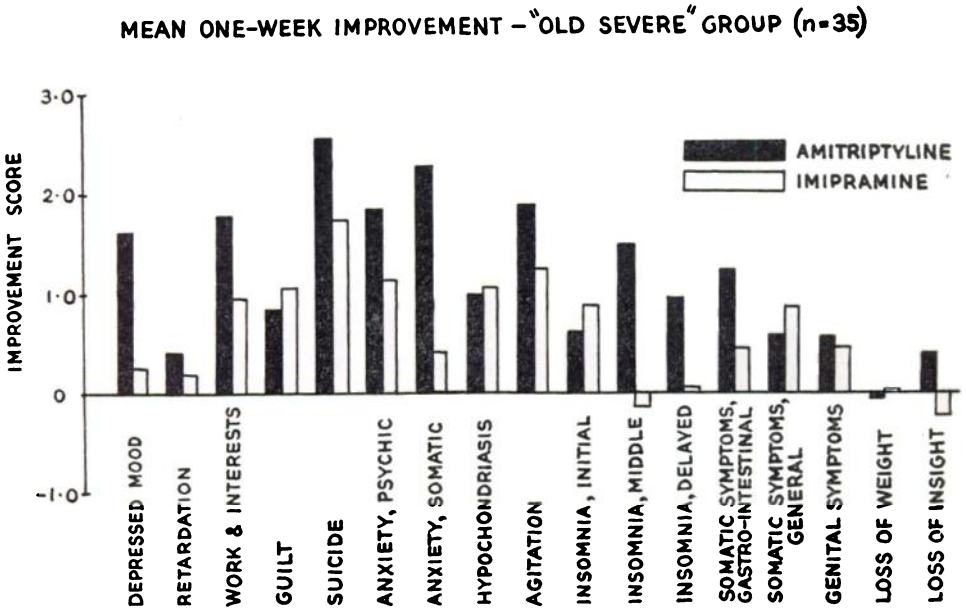


FIG. 2.

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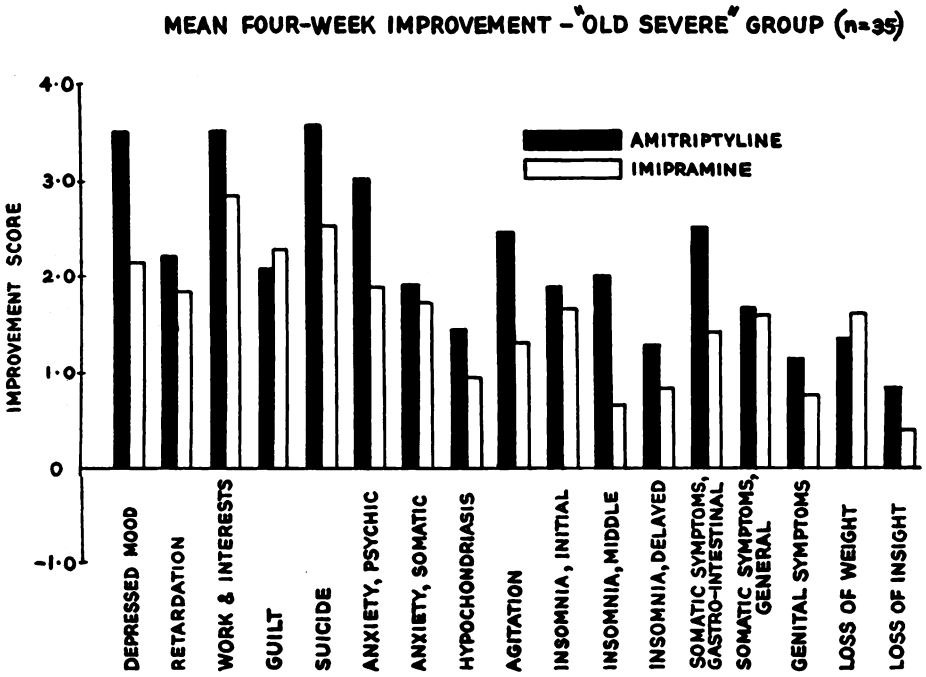


FIG. 3.

TABLE III

Significance Tests on Physicians' Ratings

(All probabilities are associated with the superiority of amitriptyline except those shown in brackets)

Symptom/ Category of Patient	After 1 Week "Old Severe" (n=35)	After 1 Week "Young Severe" (n=24)	After 1 Week Total Group (n=73)	After 4 Weeks "Old Severe" (n=35)	After 4 Weeks "Young Severe" (n=24)	After 4 Weeks Total Group (n=73)
Dep. Mood	·007†	(·06)		·05*		·06
Retardation	·14				·16	
Work & Interests	·06	(·06)		·18		·11
Guilt					·11	
Suicide	·09	(·09)		·12	(·23)	
Psychic Anxiety	·14	(·10)		·11	(·26)	
Somatic Anxiety	·008†	(·28)	·13			
Hypochondriasis		(·02)*			(·13)	
Agitation	·14	(·25)		·008†		·04*
Initial Insomnia		·16				·05*
Middle Insomnia	·008†		·05*	·02*		·08
Delayed Insomnia	·09	·11	·01†		·01†	·015*
Somatic Symptoms (Gastro-Int.)	·09	(·08)		·02*		·005†
Somatic Symptoms (General)				·40		
Genital Symptoms					·12	·05*
Loss of Weight						
Loss of Insight				·40		
Total	·02*	(·08)		·07		·014*

* Significant at 5 per cent. level.
† Significant at 1 per cent. level.

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These probabilities, together with the results of significance tests carried out in the "old severe" and "young severe" group of patients, are set out in Table III. As the "old mild" (10 patients) and "young mild" (4 patients) groups were so small, they have been omitted from the table. All differences with any reasonable possibility of being significant are shown; the figures reveal how strikingly conflicting results in the "old severe" and "young severe" groups lessened the differences shown by the total group. The picture with regard to insomnia was very consistent; all results were in favour of amitriptyline and out of 18 differences, 7 were significant ($p<\cdot05$), 3 of them highly so ($p<\cdot01$).

The superiority of amitriptyline in the "old severe" group after one week and one month of treatment is depicted for greater clarity in Figures 2 and 3.

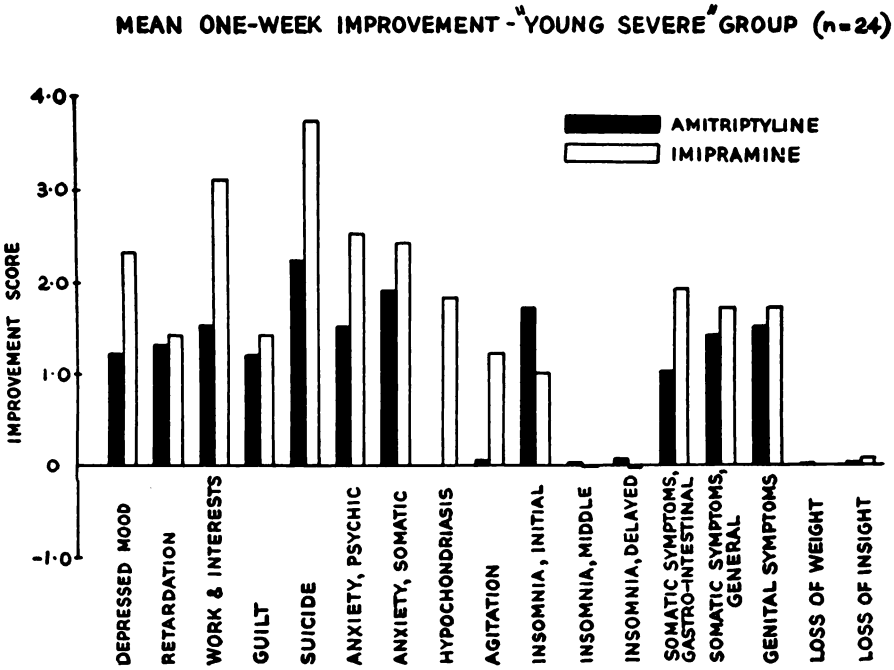


FIG. 4.

After one week amitriptyline was highly significantly superior to imipramine in ameliorating the following symptoms: depressed mood ($p=\cdot007$), somatic anxiety ($p=\cdot008$), and middle insomnia ($p=\cdot008$). The total improvement score of the amitriptyline group (19·7) was significantly higher than the imipramine-treated group (9·8) almost at the 1 per cent. level ($p=\cdot02$). After one month of treatment, amitriptyline was highly significantly superior to imipramine in improving agitation ($p=\cdot008$) and almost as superior in improving middle insomnia ($p=\cdot02$) and gastro-intestinal somatic symptoms ($p=\cdot02$). It was also significantly superior to imipramine in alleviating depressed mood ($p=\cdot05$). The total improvement score of the amitriptyline group (36·3) was not quite significantly higher than that of the imipramine group (26·3) ($p=\cdot07$).

The "young severe" group of patients exhibited quite a different picture, which was especially marked in the ratings at the end of the first week of treatment. As Figure 4 shows, after one week, the trend was for imipramine

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to be superior to amitriptyline in alleviating the symptoms of depression in this type of patient. This superiority was almost highly significant in the case of hypochondriasis ($p = \cdot 02$) and came near to significance in both depressed mood ($p = \cdot 06$) and work and interests ($p = \cdot 06$). Gastro-intestinal symptoms were more effectively relieved by imipramine at the end of a week ($p = \cdot 08$) and the total improvement score obtained with this compound (26·3) was also higher than that achieved by amitriptyline (19·2) ($p = \cdot 08$). The various types of insomnia were an exception to this general trend. At the end of a month, however, as Figure 5 shows, imipramine had lost its generalized pattern of superiority and in no symptom did its superiority reach anywhere near statistical significance. Indeed the total improvement score with amitriptyline after a month was slightly but not significantly higher than imipramine (37·6 vs 34·4). Delayed insomnia in the "young severe" group was highly significantly more effectively relieved by amitriptyline than imipramine ($p = \cdot 01$).

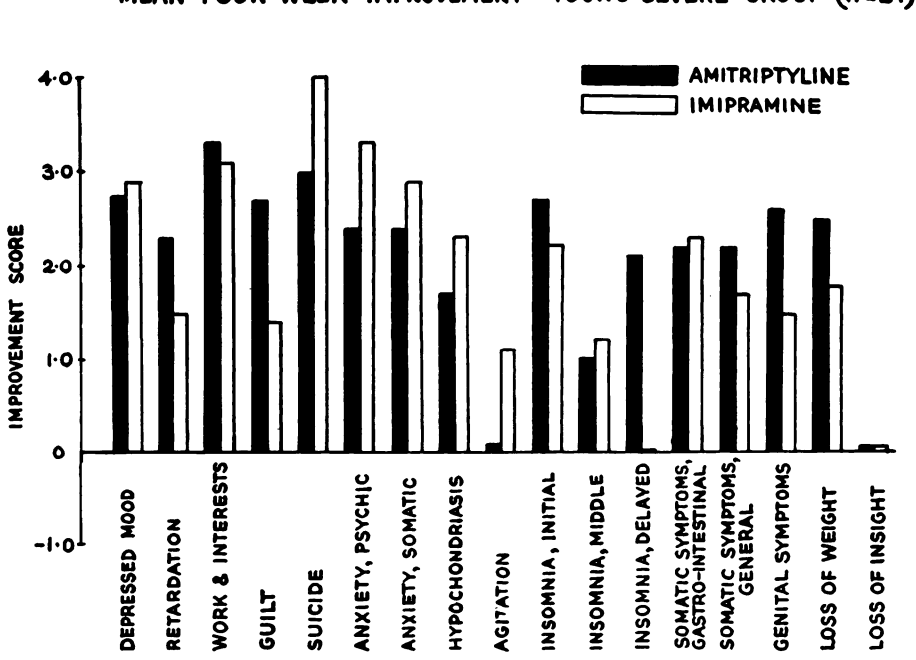


FIG. 5.

The numbers of patients in the "old mild" and "young mild" groups were too small to enable a valid comparison of the two drugs to be made, though trends could be detected in the results that were obtained. In general, after one week, the 5 "old mild" depressives on amitriptyline showed almost the same improvement in their target symptoms as did the 5 on imipramine. The mean overall improvement scores of the two groups were almost identical (10·6 vs 8·2). After a month, amitriptyline was markedly, but not significantly, better than imipramine in relieving the following symptoms: depressed mood, work and interests, hypochondriasis and gastro-intestinal somatic symptoms. By this time the mean total improvement score of the amitriptyline-treated group was appreciably higher than the imipramine group (27·8 vs 11), a difference significant at the 5 per cent. level.

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The two "young mild" depressives who received amitriptyline did better than the two on imipramine after one week and one month of treatment, but larger groups of patients would be required adequately to investigate the action of the two drugs in this type of patient.

2. *Overall Clinical Assessments*

The differences shown by the total group and the various groups of patients on the overall clinical assessments (score range 0–8) are set out in Table IV.

TABLE IV

Mean Improvement Scores on Overall Clinical Assessments

Category of Depressed Patients	Total Group		"Old Severe"		"Young Severe"		"Old Mild"		"Young Mild"	
	Amit.	Imip.	Amit.	Imip.	Amit.	Imip.	Amit.	Imip.	Amit.	Imip.
Number in drug group	n=37	n=36	n=18	n=17	n=12	n=12	n=5	n=5	n=2	n=2
1 week improvement score	1·7	1·3	2·2	1·0	1·5	1·8	1·2	1·6	2·0	0·0
1 month improvement score	3·2	2·4	3·6†	2·3	3·3	2·8	1·8	1·0	3·0	2·0

† Significant at the 1 per cent. level.

It will be noted that the overall ratings for the total group suggest that amitriptyline was more effective after one week tham imipramine; after a month the trend was more clearly evident and the difference was almost significant ($p = \cdot 06$). The one week finding is in agreement with the differences in the rating scale scores, and the overall assessments after a month reflect the significant difference in favour of amitriptyline shown by the rating scale totals. The one week improvement shown by the "old severe" group on amitriptyline was highly significantly greater than the group on imipramine ($p = \cdot 01$); this trend was still almost significant at the end of a month ($p = \cdot 07$). With the exception of the one week rating on the "old mild" group, in any group of patients at every rating period, the direction and amount of change shown by the overall clinical assessments paralleled those shown by the rating scale scores.

3. *Occupational Therapy Ratings*

Since a number of patients included in the trial were not well enough to begin occupational therapy immediately after being placed on their medications, some initial O.T. ratings could not be carried out until they had been on drugs for several days. For these patients no valid estimate of change on O.T. ratings could be made. An arbitrary decision was therefore taken not to use ratings completed more than five days after patients had started on drugs; this left 32 sets of ratings suitable for analysis. They comprised ratings on 19 patients in the "old severe" group (10 on amitriptyline) as well as 13 "young severe" depressives (6 on amitriptyline). As the two groups were so small, and as the trends of the changes they showed, unlike the physicians' ratings, were similar, they were combined to produce the results shown in Table V.

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TABLE V

Mean Improvement Scores on Occupational Therapy Ratings

Behaviour in Occupational Therapy	Possible Range of Scores	After 1 Week Amitrip. (n=16)	After 1 Week Imip. (n=16)	After 4 Weeks Amitrip. (n=16)	After 4 Weeks Imip. (n=16)
Group of instructions	0– 6	·3	– ·2	·5	– ·4
Attention to task	0– 6	·8	·3	·2	– ·1
Motivation	0– 6	·4	– ·6	·9	– ·4
Patient's self-grading	0– 6	·7	– ·4	·8	– ·2
Task Performance Sub-Total	0–24	2·2	– ·9	2·4	–1·1
Depression	0– 6	1·0	·6	1·3	·9
Retardation	0– 6	·7	·1	·9	·7
Agitation	0– 6	·2	·1	·4	– ·6
Physical complaints	0– 6	·4	·2	·5	·4
Symptom Sub-Total	0–24	2·3	1·0	3·1	1·4
Rapport with O.T.s	0– 6	·2	·2	·7	1·0
Socialization	0– 6	·4	·5	1·1	1·0
Overall attitude to O.T.	0– 6	·1	– ·3	·6	– ·1
Relationships Sub-Total	0–18	·7	·4	2·4	1·9
Total	0–66	5·2*	·5	7·9	2·2

* Significant at the 5 per cent. level.

The table shows that higher improvement scores were obtained by the patients on amitriptyline on almost all O.T. ratings, both after one week and four weeks of treatment. Sub-total and total O.T. ratings reflected strongly this general trend. Only one difference, that for the total one-week improvement, was significant at the 5 per cent. level, but the four week difference scores on task performance and depressive symptoms were almost significant ($p = \cdot 07$ and $\cdot 06$).

When the findings were examined by groups, at the end of one week the phenomena exhibited in O.T. by the "old severe" group, in every case but one, were slightly more effectively ameliorated by amitriptyline than by imipramine: the three sub-total scores were 1·8, 2·3 and 1·6 vs –1·3, 1·0 and ·2 while the totals were 5·7 vs –·1. Nevertheless none of these differences attained statistical significance. At the end of a month the same trends were maintained. The sub-total scores were 2·4, 4·3, and 3·7 for amitriptyline vs –1·4, 1·9 and 2·7 for imipramine, whilst the total amitriptyline score was 10·4 vs 3·2. None of these differences however were statistically significant.

At the end of one week the "young severe" depressives showed a tendency for amitriptyline to be slightly more effective in alleviating the phenomena itemized on the rating scale; this time however the three items comprising "relationships" showed a little more improvement with imipramine. The sub-total scores were: amitriptyline 3·2, 2·5 and –·5 vs –·4, 1·0 and ·7 for imipramine; the total scores were amitriptyline 5·2 vs imipramine 1·3, again an insignificant difference. After a month amitriptyline did better in almost all the items on the scale; sub-total scores were 2·3, 1·2 and 0 vs –1·4, 1·0 and 1·0 for imipramine. The total score for amitriptyline was 3·5 vs ·6, again a superiority for amitriptyline, but a statistically insignificant one.

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4. *Side-Effects Ratings*

Systematic ratings were completed on 70 female patients, 35 on amitriptyline and 35 on imipramine. In an oral dosage of 150 mg. daily for one week, followed by 200 mg. daily for 3 (or sometimes 5) weeks, both drugs were safe, well tolerated and non-toxic. In this dosage range the side-effects of amitriptyline were almost identical with those of imipramine; there were no significant differences between them, nor even any distinctive trends. With both drugs, side-effects were very mild and easily tolerated; they diminished or disappeared after 3 weeks of treatment and were quite unrelated to age. Their incidence before and after drug treatment is shown in Figure 6. In examining this figure, however, it should be noted that it depicts only the incidence of side-effects, and provides no guide to their severity. The high incidence of reactions shown in the figure is comprehensible in the light of the fact that each patient received 12 (or more rarely 18) systematic side-effect examinations; even one point (on a four point scale) registered on only one occasion would constitute an addition to the horizontal lines of incidence from which the figure is composed.

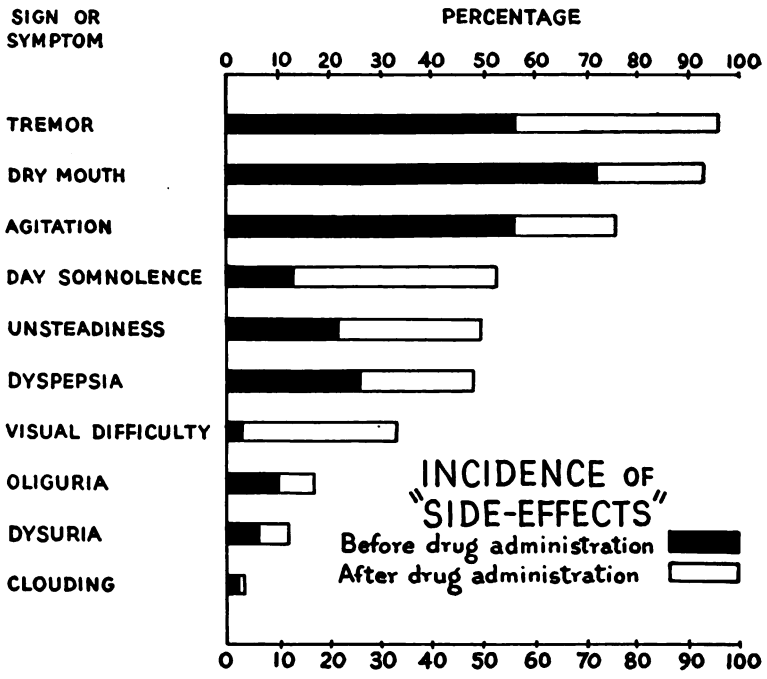


FIG. 6.

With the aid of Figure 6 it is readily possible to separate side-effects into three groups, the separation being made in terms of the incidence of each side-effect before the administration of either medication. Group 1—"visual difficulties" (mainly blurred vision) and "somnolence" can appropriately be regarded as true side-effects of amitriptyline and imipramine. Group 2—"unsteadiness" (faintness, dizziness and ataxia), "dyspepsia" (heartburn, nausea and vomiting) and "urinary difficulties" (dysuria and oliguria) appear just as likely to be symptoms of depression as to be side-effects. The reactions included in Group 3—"tremor", "dry mouth" and "agitation"—are probably symptoms of depression rather than side-effects of the two drugs.

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5. Outcome of Treatment

The two following tables show the results obtained in the 73 patients according to the numbers that were discharged after four and six weeks with or without E.C.T. and according to the response of endogenous and reactive depressives to the two drugs.

TABLE VI

Outcome of Treatment by Drug Groups

	Amitriptyline	Imipramine
4 week discharge	22*	17
ECT	5	12
6 week discharge	7	4
ECT	3	3
Overall discharge	29*	21
ECT	8	15

* Significant at 6 per cent. level.

The differences between the drugs at four weeks as well as over the total period in terms of discharge very nearly reached statistical significance ($p = \cdot 06$). In those patients who, failing to respond to drugs, were given E.C.T., the actual number of electroconvulsive treatments administered was decided by physicians other than those involved in the trial. Despite reports to the contrary from other investigators, there was no evidence that, in the present investigation, fewer treatments than are customary were sufficient to ameliorate the depressive states of patients who had had courses of either of the two drugs.

The results of drug treatment in terms of outcome according to type of depressive illness are shown in Table VII.

TABLE VII

Outcome of Treatment by Type of Depression

	Endogenous		Reactive	
	Amitrip.	Imipr.	Amitrip.	Imipr.
Discharge ..	18*	9	11	12
E.C.T.	7	11	1	4

* Significant at 5 per cent. level.

The difference between the drugs in the endogenous depressives attained statistical significance ($p = \cdot 04$). In the reactive group both drugs were effective, though amitriptyline was noticeably—though not significantly—superior.

DISCUSSION

A clinical study of the effects of drugs on depressive disorders, as Freyhan (1960) has pointed out, necessitates the identification of specific "target symptoms" on which the drugs may be expected to act. Such an analysis of symptoms reduces the possibility of real differences between treatments being overlooked, as can occur if crude "overall clinical assessments" are used. Freyhan has also observed that drug treatment, in contradistinction to E.C.T., allows of experiential continuity and more complete patient participation. In this way patients, unhampered by amnesia, can accurately describe their symptoms at any point in time. In measuring and quantifying the changes in

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these depressive "target" symptoms, Hamilton's scale proved very valuable. A simple instrument, it took but little time to use, and its reliability was attested by an inter-rater agreement of 0·85; mean scores were 25·72 and 27·01 with standard deviations of 6·9 and 6·4; the differences between the two raters' ratings were not statistically significant. The validity of the scale is apparent from the finding that a drop in the score corresponded in the great majority of cases with improvement as recorded by overall clinical assessments and with falling scores in the occupational therapy ratings. In 95 per cent. of cases a final score of 10 or less corresponded to discharge. The use of the scale enabled a number of statistically significant drug differences in the alleviation of target symptoms to be readily demonstrated, a result that would not have been possible if reliance had been placed entirely on overall clinical assessments or on numbers of patients discharged.

Stratification of patients by age and severity of illness proved very useful, for both variables quite markedly affected the response to the two drug treatments. Older patients with more severe illnesses responded appreciably better to amitriptyline than to imipramine. This trend appeared to be correlated more with chronological age than with the menopause. Though all the patients over 50 who responded well were post-menopausal, several younger women who had undergone a natural or an artificially-induced menopause responded less well than those over 45 years of age. This topic will be discussed in more detail in a later paper.

It is interesting to note that the occupational therapy rating scale scores tend in general to conform with the Hamilton scale ratings and the overall clinical assessments. The slight superiority shown by imipramine on these instruments in the one week rating on the "young severe" depressives was not, however, paralleled in the O.T. ratings. In this connection, there is no evidence that the three instruments were, in fact, measuring similar forms of behaviour; the scatter of the O.T. scores was very wide; the times at which the O.T. scale ratings were made were not as accurately tied to the schedule of drug administration as the other two ratings; and the occupational therapists had had less opportunity to practise with their scale than had the physicians. In practice, the scale was simple to use and rapidly completed; inter-rater agreement produced a correlation coefficient of ·90. The close parallel between the results on the physicians' scale and on the O.T. ratings is further evidence of the reliability of the general finding in favour of amitriptyline.

Throughout the study, no patient had to have her dosage reduced because of side-effects, which were remarkable only by their paucity and mildness. In this connection, the mildness and triviality of side-effects in imipramine-treated in-patients has been remarked on by Kenning *et al.* (1960) and is in sharp contrast to the 83 per cent. of side-effects, many of them troublesome, reported by Kiloh & Ball (1961) with out-patients treated with the same drug. In amitriptyline-treated cases fairly numerous though subjectively less severe side-effects have been reported by Ayd (1961) and Pressman and Weiss (1961) Nevertheless, as the present investigation shows, some "side-effects" are probably part of the depressive syndrome rather than products of drug administration. The comparative troublesomeness of the side-effects encountered by these other investigators may well have been due to the high proportion of cases they treated as out-patients. In the present study, in terms of the production of side-effects, amitriptyline, in female in-patients in oral dosages of 200 mg. daily, showed no superiority over imipramine. The investigation did however confirm the mildness of side-effects on in-patients

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treated with either drug, and drew attention to the difficulty of distinguishing between pure side-effects and concomitant symptoms of depressive illness.

The use of the designation "depressive state" to categorize the 73 patients included in the trial was an attempt to avoid the semantic difficulties inherent in selection based on more usual designations such as "melancholia", "endogenous", "reactive" and "involutional" depressions. However, the majority of patients allocated to the "severely depressed" group (i.e. with initial rating scores of 40 or more) were independently given clinical diagnoses of "endogenous depression"; those allocated to the "mildly depressed" group (with initial scores below 40) most frequently were diagnosed as "reactive" (a term which, for present purposes, includes "neurotic" depression). Nevertheless, since this correspondence between severity and diagnostic grouping was far from exact, and since many psychiatrists prefer to classify depressions into "endogenous" and "reactive" types, an attempt was made to allocate each patient to one or other group. As might have been expected a proportion of diagnoses—in this case 14 per cent.—were in dispute, and in these 10 patients a forced choice had to be made in terms of the preponderance of commonly used differentiating criteria. Judgments were made independently by two of the authors (C.G.B. and W.F.G.) who were unaware of the drugs received by the patients they classified. In the event, amitriptyline was significantly superior to imipramine ($p = \cdot 04$) in alleviating the symptoms of endogenous depressives: it was also superior in reactive cases, though in this case statistical superiority could not be demonstrated.

Perhaps the most convincing criterion of the efficacy of an antidepressant drug is the percentage of depressed patients who, after treatment with it, can be discharged well without requiring E.C.T. Judged by this criterion, in the present trial 78 per cent. of the amitriptyline cases improved in contrast to 58 per cent. of the imipramine treated patients. The latter figure is almost identical with the 60 per cent. improvement noted in in-patients treated with imipramine by Kenning *et al.* (1960), but is lower than the 74 per cent. improvement rate shown by out-patients given imipramine by Ball and Kiloh (1959). In his comparative study of antidepressants, Ayd (1960) found that 79 per cent. of 130 amitriptyline-treated cases, some of them out-patients, improved, in contrast to 73 per cent. of 100 patients treated with imipramine. Pressman and Weiss (1961), who treated 100 "ambulatory" patients with amitriptyline and 100 with imipramine, reported that 79 per cent. improved in the former group, against 75 per cent. in the latter group. However in Ayd's and Pressman and Weiss's patient sample, a largish proportion of patients not suffering from pure depressive syndromes was included, and Ayd mentions combining amitriptyline with E.C.T. and tranquillizers on some occasions. Such factors may explain the failure of these latter investigations to demonstrate the superiority of amitriptyline as convincingly as does the present investigation.

Finally, the trial demonstrates rather clearly the complementary nature of "open" and "controlled" methods of investigating the effect of drugs. Though the proponents of each type of investigation are apt to criticize each other, it is apparent that both types of study are necessary, the first to lay groundwork and to obtain preliminary clinical impressions, the second to confirm the findings of the open study and to subject them to more precise intensive scrutiny. With the exception of the findings on side-effects, the present controlled trial would seem to confirm the majority of the impressions obtained from earlier open investigations of amitriptyline as well as furnishing additional data for research into the action of antidepressant compounds.

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Summary and Conclusions

1. Preliminary studies on amitriptyline, a new antidepressant resembling chlorpromazine and imipramine, are reviewed, and a double blind controlled comparison of amitriptyline and imipramine in 73 female depressives between 30 and 70 years of age hospitalized for a month (or more rarely six weeks) is described. Patients included in the trial were allocated by age and severity of illness (according to rating scale scores) into four categories; "old severe", "young severe", "old mild" and "young mild" groups. A scale score of 40 (out of a total sum of 100) was the borderline separating "mild" from "severe" cases; "young" patients were aged 30–49 whereas the "old" group comprised patients between 50 and 70.

2. After receiving amitriptyline or imipramine in oral doses of 150 mg. daily for one week, all patients received 200 mg. daily for a further three (or occasionally five) weeks. Each patient was evaluated initially as well as after one and four (and occasionally six) weeks by means of (1) a rating scale for depression; (2) an overall clinical assessment; and (3) an occupational therapy rating scale. Side-effects were recorded thrice weekly on a specially constructed scale, and at the end of four (or occasionally six) weeks, the outcome was recorded in terms of discharge or referral for E.C.T.

3. The results of the various modes of assessment corresponded very closely and showed that over the total group of patients amitriptyline was superior to imipramine in alleviating most of the symptoms of depression. This superiority, evident though slight after one week, was well marked after a month of drug treatment. The trend was particularly evident amongst the "old severe" group of patients, who showed statistically significant improvement on both rating scale scores and overall clinical assessments. An opposite, though not statistically significant, trend was shown on these two measures of change by the "young severe" patients after one week; but in these patients after a month, amitriptyline paralleled imipramine in therapeutic efficacy. Results in the "old mild" and "young mild" groups, which unfortunately were too small for valid comparisons to be made, also tended to suggest that amitriptyline was more effective than imipramine. In relieving the various types of insomnia in every category of patient included in the trial, amitriptyline was significantly superior to imipramine. On the other hand, in regard to the production of side-effects, no superiority for amitriptyline could be demonstrated, and these symptoms, which occurred equally in both groups, were remarkable only for their paucity and triviality; many, rather than constituting true side-effects, were part of the depressive syndrome itself.

4. As judged by outcome of treatment in terms of discharge or the need for E.C.T., amitriptyline, which relieved 78 per cent. of patients, was clearly and almost statistically significantly ($p = \cdot 06$) superior to imipramine, which relieved 58 per cent. Amitriptyline was also significantly ($p = 0 \cdot 04$) superior to imipramine in the treatment of endogenous depressives. Both drugs were effective in reactive cases. Overall, the results of the present trial convincingly suggest that, amitriptyline is the most effective drug currently available for the treatment of female patients hospitalized with depressive states.

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References

ALEXANDER, L. (1961). *Dis. Nerv. System*, **22**, 14 supp.
ASHBY, W. R., COLLINS, G. H. (1961). *J. Ment. Sci.*, **107**, 547.
AYD, F. J. (1960). *Psychosomatics*, **1**, 1.
Idem (1961). *Dis. Nerv. System*, **22**, 32 supp.
BALL, J. R. B., KILOH, L. J. (1959). *Brit. Med. J.*, *ii*, 1052.
BARSA, J. A., SAUNDERS, J. G. (1961). *Am. J. Psychiat.*, **117**, 739.
BRUCE, E. M., CRONE, N., FITZPATRICK, G., FREWIN, S. J., GILLIS, A., LASCELLES, C. F., LEVINE, L. J., MERSKEY, H. (1960). *Am. J. Psychiat.*, **117**, 76.
CADE, J. F. J., KRUPINSKI, J. (1961). *Med. J. Austral.*, 400.
DORFMAN, W. (1960). *Psychosomatics*, **1**, 153.
Idem (1961). *Dis. Nerv. System*, **22**, 41 supp.
DOUST, J. W. L., LEWIS, D. J., MILLER, A., SPROTT, D., WRIGHT, R. L. D. (1959). *Canad. Psychiat. Assoc. J.*, **4**, 190 supp.
DUNLOP, E. (1961). *Dis. Nerv. System*, **22**, 49 supp.
FELDMAN, P. E. (1961). *Dis Nerv. System*, **22**, 27 supp.
FREED, H. (1960). *Am. J. Psychiat.*, **117**, 455.
FREYHAN, F. A. (1960). *Am. J. Psychiat.*, **116**, 1057.
GILLESPIE, R. D. (1926). *Brit. Med. J.*, *ii*, 878.
HAMILTON, M. (1960). *J. Neurol. Neurosurg. and Psychiat.*, **23**, 56.
HOLT., J. P., WRIGHT, E. R., HECKER, A. O. (1960). *Am. J. Psychiat.*, **117**, 533.
HUSTON, P. E. and LOCHER, L. M. (1948a). *Arch. Neurol. Psychiat.*, **59**, 385.
Iidem (1948b). *Arch. Neurol. Psychiat.*, **60**, 37.
KENNING, I. S., RICHARDSON, N. L. and TUCKER, F. G. (1960). *Canad. Psychiat. Assoc. J.*, **5**, 60.
KILOH, L. G. and BALL, J. R. B. (1961). *Brit. Med. J.*, *i*, 168.
LEHMANN, H. E., KAHN, C. H. and DE VERTEUIL, R. L. (1958). *Canad. Psychiat. Assoc. J.*, **3**, 155.
LEHMANN, H. E. (1959). *Canad. Psychiat. Assoc. J.*, **4**, 1 supp.
LEWIS, A. J. (1934). *J. Ment. Sci.*, **80**, 277.
LEYBERG, J. T. and DENMARK, J. C. (1959). *J. Ment. Sci.*, **105**, 1123.
MAPOTHER, E. (1926). *Brit. Med. J.*, *ii*, 872.
OSTEFELD, A. M. (1961). *Dis. Nerv. System*, **22**, 24 supp.
PRESSMAN, M. D. and WEISS, L. B. (1961). *Am. J. Psychiat.*, **118**, 74.
REES, L. (1960). *Nature*, **186**, 114.
Idem, BROWN, A. C. and BENAIM, S. (1961). *J. Ment. Sci.*, **107**, 552.
ROGERSON, C. H. (1940). *J. Ment. Sci.*, **86**, 632.
ROTH, M. (1959). *Canad. Psychiat. Assoc. J.*, **4**, 32 supp.
ROTHMAN, I., GRAYSON, H. and FERGUSON, J. (1961). *J. Neuropsychiat.*, **2**, 158.
SARGANT, W. (1961). *Brit. Med. J.*, *i*, 225.
SIEGEL, S. (1956). Nonparametric Statistics. London: McGraw-Hill.
SLOANE, R. B., HABIB, A. and BATT, U. E. (1959). *Canad. Med. Assoc. J.*, **80**, 540.
STOLLER, A. (1960). *Med. J. Austral.*, 413.
VAISBERG, M. and SAUNDERS, J. C. (1961). *Dis. Nerv. System*, **22**, 334.
VERNIER, V. G. (1961). *Dis. Nerv. System*, **22**, 7 supp.
VON ARNOLD, O. H. and FOITL, G. (1961). *Wien. med. Wchnschr.*, **111**, 272.
ZELCER, I. (1961). *El Dia Medico*, **33**, 424.

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