Papers and Originals

Depressive Illness in a General Practice. A Demographic Study and a Controlled Trial of Imipramine

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Summary: The distribution of 93 consecutive cases of depressive illness in a Surrey general practice was found to be non-random. Married women were at risk, while men and unmarried women were largely spared. Married women were prone to the disorder at any time in their lives, and relapse was frequent. There was some suggestion that divorced wives and wives of low social class were particularly predisposed to the disorder.

Sixty of the patients took part in a double-blind controlled trial of imipramine. There was no evidence that the drug was superior to a placebo in inducing a remission. It is suggested that imipramine has become established in clinical practice on inadequate evidence and that there is a need for further trials.

Introduction

This study deals with patients who presented with a depressive illness in one general practice over a three-year period. The main object is to evaluate the effectiveness of imipramine in the treatment of the type of depression met in general practice; the record-keeping associated with the clinical trial provides an opportunity to undertake also a companion demographic study.

Depression is a "non-hospital disease" (Fry, 1961); only a small proportion of patients find their way to psychiatric outpatient departments (Bodkin *et al.*, 1953; Leigh, 1955; Watts, 1956; Kessel, 1960; Taylor and Chave, 1964; Shepherd *et al.*, 1966). Hence epidemiological studies of the disorder can be done only from general practice, for the hospital impression may often be distorted. Many psychiatric morbidity studies have been published, but these have been concerned with prevalence rather than epidemiology (see Silverman, 1968). Others—for example, Watts (1966)—are concerned to describe the nature and frequency of depressive illnesses encountered in the community. The authoritative study of Shepherd *et al.* (1966) into psychiatric illness in general practice does not lessen the need for further work in an attempt to unravel the demographic details of depressive illnesses.

The practice in which this study took place is 30 miles (48 km.) from London and comprises a young "overspill" and "infilling" population grafted on to an established "indigenous" one, and contains a wide range of socioeconomic groups.

PART I. EPIDEMIOLOGY

The problem of the classification of depressive illnesses is generally acknowledged. No attempt was made to place patients into categories such as "neurotic," "endogenous," or "involutional"; patients were admitted to the study if they suffered from a sustained affective illness in which depression of the mood was prominent. The occasional patient suffering from depression secondary to a psychosis was not included.

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Two difficulties must be acknowledged. The first relates to the role of anxiety. All patients within the spectrum of mixed depression and anxiety were admitted to the study, but those whose illness fell wholly at one end of the spectrum, with extreme anxiety, phobias, and somatic symptoms, and who would not admit to any depression, were excluded. This decision is conventional, probably illogical, and certainly arbitrary. The second difficulty relates to reactive depression. This is a nosological entity whose reality must be conceded. If, following bereavement or misfortune, the patients' depression seemed appropriate and potentially self-limiting they were not admitted. If, on the other hand, their reaction seemed inappropriate, too profound, and oversustained, they were admitted. Only 10 out of 93 (11%) fell into this category.

Characteristics of Patients Studied

A practice census, undertaken during the first year of the study, enables a comparison to be made between the population with depression and the practice population.

Age–Sex Distribution.—Of the patients with depression there was an excess of women over men; of the 93 patients, 79 (85%) were women. This difference was a real one (Table I).

TABLE I.—*Sex Distribution of Depressed Patients Compared with Practice Adults*

	Men	Women	Total
Depressed Patients	14	79	93
Practice Adults (>15 years old)	808	1,011	1,819

$\chi^2 = 29{\cdot}2$; D.F. = 1; $P < 0{\cdot}001$

The age distribution of both the women with depression and all women in the practice was normal and of comparable profile (Fig. 1). The mean age of the women with depression (39·5 years, S.D. 13·3) was very similar to that of the women in the practice (41·1 years, S.D. 18·6); the difference was not significant ($t = 0{\cdot}74$; $0{\cdot}25 > P > 0{\cdot}2$).

Prevalence.— During the survey 93 patients attended with a depressive illness. This represents a patient consulting rate—the number of patients per 1,000 adult population who consulted at least once, see Logan and Cushion, 1958—of 51·1 for both sexes, 17·3 for men and 78·1 for women. The annual incidence was 19·2 per 1,000 persons at risk for both sexes—6·5 for men and 29·3 for women. About 1 in 13 of women in the practice attended at least once during the 32 months of the survey on account of a depressive illness; if single women were excluded the ratio was 1 in 10 (Table II).

TABLE II.—*Marital Status of Depressed and Practice Patients*

	Women		Men	
	Depressed	Practice	Depressed	Practice
Married	67	625	12	572
Single	1	199	2	154
Widowed	6	124	0	20
Divorced or separated	5	10	0	8
Uncertain	0	53	0	54
Total	79	1,011	14	808

Marital Status.—Patients were allotted to one of five groups: married, single, widowed, separated or divorced (and not remarried), and "marital status uncertain" (Table II). The number of men with depression was small, but the distribution between the categories seemed comparable to that of the practice as a whole. Among women there was an excess of married ones ($\chi^2 = 16{\cdot}2$; D.F. = 1; $p<0{\cdot}001$); single women are spared, and separated or divorced ones are at risk, though the large "uncertain" group in the practice lessens the significance of the last finding.

Housing.—The "indigenous" population, now in a minority in the practice, have roots which extend back to the prewar town. The "infilling" population have arrived during the past 10 years to buy private houses or to rent flats, and to commute to London and other places of work. The "overspill" scheme of the past few years has absorbed some London families with housing problems and has resettled them in a local housing estate.

The distribution of the practice and depressed populations is examined in Table III. The numbers expected on the null hypothesis of no difference are given in parentheses. There is an excess of depressed patients in the overspill group and a deficiency in the indigenous group.

Social Class.—Each head of household was placed into a "manual" or "non-manual" category according to occupation. Of these 793 persons, 295 (37%) were defined as manual workers, 325 (41%) as non-manual workers, and in 173 (22%) the allocation was uncertain. In the case of women with depression the position was reversed: 48 out of 79 (61%) were in the manual category and 31 (39%) were non-manual.

Size of families.—The mean size of family was 1·5 children. For comparison, an analysis of the families of 25 married women randomly chosen from the practice showed a mean family size of 2·3 children.

Premenstrual Tension.—Data were examined to determine whether women were prone to present with depression during the premenstrual week. Of the 43 women who still menstruated, data were available for 37 (86%). If it is accepted that the average menstrual cycle lasts about four weeks (Gunn *et al.*, 1937; Fluhmann, 1956; Chiazze *et al.*, 1968), then, on the null hypothesis of no premenstrual predisposition to the presentation of depression, about nine patients should have attended for the first time during the premenstrual week. The actual number was 13. Treatment of the distribution as binomial, with the probability (P) equals one-quarter, then the probability of 13 or more patients attending in the premenstrual week was 19·4%. The difference between the expected and actual number was therefore not significant.

Blood Groups.—The blood groups of the 93 depressed patients are shown in Table IV.

Physique.—The main indices of physique are shown in Table V.

Relapse Rate.—Information about the relapse rate was available for 85 out of the 93 patients; 29 (34%) had suffered a recurrence within one year of their attendance and 56 were still in the practice, but had not reattended with depression. One patient had died and data were not available for seven patients.

Dissatisfaction.—During 1965 22 out of 1,625 adult patients were categorized as "dissatisfied," having left for another practice in the district. Seventy-eight patients in the practice were known to have had a depressive illness at some time, and 6 out of the 22 dissatisfied patients came into this category; this was a highly significant excess ($P<0{\cdot}001$). It was also found that over a period of years 144 adults had joined the practice from neighbouring colleagues. Of these, 18 were known to have had a depressive illness; this also is a highly significant excess ($P<0{\cdot}001$). Clearly all doctors are involved in the discontent of these patients (Porter, 1966).

TABLE III.—*Distribution of Depressed Patients in Various Demographic Categories*

	Overspill	Indigenous	Infilling
Depressed	31 (20·6)	22 (31·7)	40 (40·7)
Practice: heads of household*	164 (174·4)	278 (268·3)	346 (345·2)

*Allocation uncertain, n = 5. $\chi^2 = 9{\cdot}1$; D.F. = 2; $0{\cdot}01 < P < 0{\cdot}02$

TABLE IV.—*Blood Groups of the 93 Depressed Patients and Two Control Groups*

		Depressed Group	Practice Antenatal Patients	Surrey*
ABO Group:				
A	No.	42	187	5,700
	%	47·8	44·5	42·18
B	No.	8	26	1,176
	%	9·1	6·2	8·7
AB	No.	3	16	420
	%	3·4	3·8	3·1
O	No.	35	191	6,217
	%	39·8	45·5	46·01
?	No.	5	—	—
Rh Group:				
Rh positive	No.	69		
	%	78·5		
Rh negative	No.	19		
	%	21·5		
?	No.	5		

*Figures kindly supplied by Dr. Ada Kopeć

TABLE V.—*Data in Respect of the Main Indices of Physique*

		Number	Mean	S.D.
Nude weight (lb.)	Male	13	154·2	23·1
	Female	73	131·8	29·1
Height (in.)	Male	13	68·1	2·5
	Female	72	63·7	2·5
Subcutaneous fat over left triceps (mm.)	Male	13	8·19	6·26
	Female	69	18·21	7·44
Ponderal index	Male	13	12·75	0·72
	Female	72	12·46	0·89

Discussion

This study once more emphasizes how frequent depressive illnesses are in general practice. The incidence of 19 per 1,000 per annum in my practice broadly compares with rates found in many other surveys (see Watts, 1966). Any incidence derived from a general practice morbidity study must underestimate the true incidence in the populace, for some patients will not consult their doctor and will remain unrecorded.

The high relapsing rate is consistent with other reports (Pedersen *et al.*, 1948; Oltman and Friedman, 1964; Beck, 1967), as is also the finding of an excess of women over men in patients with depression (Paskind, 1930; Bremer, 1951; Fry, 1952; Watts, 1956; Crombie, 1957; Essen-Möller and Hagnell, 1961; Helgason, 1961; Sørensen and Strömgren, 1961; Cooper *et al.*, 1962; Kessel and Shepherd, 1962; MacKinnon, 1966).

The most important and clear-cut finding in this study is that single women are almost entirely spared from depressive illnesses and married ones are particularly at risk. On the null hypothesis of no difference 15 single women should be found in the depressed group, while in fact only one is found. By contrast, Shepherd *et al.* (1966) found that the rate for married women did not differ from that for single ones. The discrepancy is not readily explicable.

Most, but not all, writers on this subject have agreed that psychiatric morbidity in general, and depressive illnesses in particular, are more common in middle life (Fry, 1952; Crombie, 1957; Cooper *et al.*, 1962; Shepherd *et al.*, 1966; Watts, 1966). If, however, the necessary comparison is made between the age distributions of my practice and the depressed patients (Fig. 1) a similar profile is found; no age group was particularly at risk. This finding confirms that of two other surveys (Juel-Neilsen *et al.*, 1961; Sørensen and Strömgren, 1961).

There was no evidence in my study that women were particularly prone to attend with depressive illnesses during the

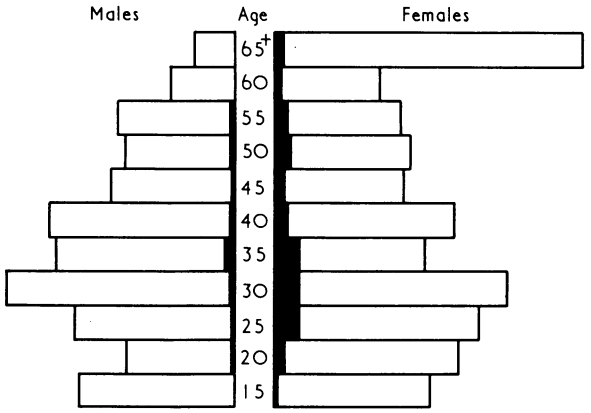

FIG. 1.—Age distribution of practice and depressed patients.

premenstrual week. This negative finding compares with observations that suicides, accidents, and deaths are more common during this time (MacKinnon and MacKinnon, 1956), as are also psychiatric illnesses (Dalton, 1959), including depression and anxiety (Coppen, 1965).

The patients with depression were not distributed randomly between the three different housing groups; the excess of depressed patients in the infilling population and the deficiency in the indigenous population are both facts which are unlikely to have arisen by chance. It cannot, however, be concluded that the inhabitants of a new housing estate are particularly prone to depressive illnesses because they have recently moved district, for the demographic details of the two populations were quite different. There is now general agreement that new-town populations are not, in fact, particularly prone to mental illnesses (Taylor and Chave, 1964; Hare and Shaw, 1965). There was no evidence that caring for a large family predisposed a mother to a depressive illness.

The observation that depressed patients are particularly liable to change their doctor is not original; in 1661 Riverius wrote: "It is also called the Scourge of Physitians, because they who have it are continually asking new Medicines, and presently wearied therewith, and dayly complain to the Physitians and often change them."

An increased incidence of blood group O in depressive illnesses has been suggested (Parker *et al.*, 1961; Irvine and Miyashita, 1965; Masters, 1967), but Raphael *et al.* (1927) found no evidence of a relationship. Manuila (1958) emphasized that comparisons of blood groups between patients and control subjects are fraught with difficulties and that sampling errors may be higher than supposed. Thus no conclusion can be drawn from my small series, but the figures are recorded in case it might be possible to incorporate them in a larger one.

Since no anthropometric normal values have been recorded for Britain (Patch *et al.*, 1965; Coppen *et al.*, 1966) it is impossible to draw any conclusions about a possible relation between depression and physique; it seems, none the less, worth while recording these figures. In fact, they have retrospectively yielded one possible association—namely, that women who volunteered side-effects while taking imipramine were significantly taller than those who did not. This may indicate that both the rate of metabolism of imipramine and body height are influenced by the same genes (Porter, 1968).

In the practice census it was found impossible to allocate as many as one in five adult patients into the simple classification of social class. Shepherd *et al.* (1966) met a similar difficulty and could find no simple association between social class and psychiatric morbidity. My survey suggests that depression may be more common in wives married to manual workers than in those married to non-manual ones, but the evidence is weak owing to the limitations of the census.

PART II. CONTROLLED TRIAL OF IMIPRAMINE

Imipramine was introduced as an antidepressant drug in 1958. Since then 24 placebo controlled trials have been published, but only five of these (Ball and Kiloh, 1959; Daneman, 1961; Abraham *et al.*, 1963; Medical Research Council, 1965; Bassa and Vora, 1965) have been concerned wholly or partially with outpatients and none has originated from a general practice. Five out of the 24 trials have returned adverse verdicts (Doust *et al.*, 1959; Sloane *et al.*, 1959; Roulet *et al.*, 1962; Bassa and Vora, 1965; Friedman *et al.*, 1966). In the remainder (Lehmann *et al.*, 1958; Ball and Kiloh, 1959; Leyberg and Denmark, 1959; Holdway, 1960; Kenning *et al.*, 1960; Miller *et al.*, 1960; Agnew *et al.*, 1961; Ashby and Collins, 1961; Daneman, 1961; Friedman *et al.*, 1961; Höhn *et al.*, 1961; Linford Rees *et al.*, 1961; Rothman *et al.*, 1961; Overall *et al.*, 1962; Wittenborn *et al.*, 1962; Abraham *et al.*, 1963; Robin and Langley, 1964; Medical Research Council, 1965; Schorer *et al.*, 1966) the verdicts are either generally favourable or else the allocation is difficult.

It is disturbing that three out of five of the unfavourable trials have been published since 1961, the modal year if the trials are charted according to their year of publication; no trial has been published since 1966. Contradictory reports should be an indication for further work (Beck, 1967); instead, adverse verdicts have coincided with a waning interest and the drug has gained—on inadequate evidence—an established, if ill-defined, place in psychiatry.

About 7 out of 10 tablets of imipramine dispensed in the United Kingdom are prescribed by general practitioners. Hence there is a particular need and responsibility to put into practice the dictum that "drugs which are to be used in general practice should be assessed in general practice" (Noel, 1964).

This paper describes a controlled trial of the drug undertaken from my general practice.

Method

Patients were considered for admission to the trial if they suffered from an affective illness with sustained depression. They were excluded if the severity of the illness justified referral, if the depression was an aspect of a psychotic illness, if an antidepressant drug had been taken, or if electric convulsion treatment had been administered within the previous year. An escape clause allowed the prompt removal of a patient whose condition deteriorated and who required admission to hospital, or if it became evident that the original diagnosis of mental illness was incorrect and that an underlying organic illness was responsible for the symptoms. If, on the other hand, a patient made a rapid recovery she could be discharged two weeks after starting treatment, one week before the end of the three-week trial, but this proved to be exceptional. If a drug is to be clinically useful in a naturally remitting disorder it is important that it should work reasonably quickly; a short duration for the trial was therefore deliberately chosen.

In all a total of 60 patients contributed wholly or partially to the assessment (Table VI).

TABLE VI.—*Fate of a Cohort of 93 Patients Presenting with a Depressive Illness*

No. attended		93
Excluded	11	
Escape clause	6*	38
Defaulters:		
Overt	19	
Occult	2	
Complete data		55

*Five of the six patients removed in accordance with the escape clause contributed some useful data.

Detection of Defaulters and Dosage

Defaulting may be of two kinds—"overt" and "occult." In the former the patient fails to reattend or admits to failing to take her tablets. In occult defaulting the patient appears to the unwary to be co-operative or "compliant," when the truth is the opposite; such defaulting will not be detected unless it is searched for. All drug trials undertaken on unsupervized patients should therefore incorporate methods of detecting drug defaulters. The methods used in this trial have been described elsewhere (Porter, 1969), and consisted of tablet-marking with riboflavine and a discrepancy estimate. In this trial 19 patients were overt defaulters and two were identified as occult (Table VI). Complete data were therefore available for 55 patients.

Tablets and Dosage

Tablets of four different compositions were used: placebo alone, placebo plus riboflavine (6 mg.), imipramine (25 mg.), and imipramine (25 mg.) plus riboflavine (6 mg.). All were similar in appearance and were coated with yellow sugar to ensure that no staining of the shell occurred from the vitamin content. Only half the tablets were marked with riboflavine in order to permit the final analysis of the data to exclude interaction of riboflavine and imipramine at the enzymic level (Richter, 1961). The starting dose was one tablet three times a day. If at the end of the first week the response to treatment was indifferent the dose was increased to two tablets three times a day. Code letters were allotted to each type of tablet by the drug firm, and the code was not broken until after the statistical analysis was completed.

Inception Procedure

A form was completed as soon as the diagnosis was considered; on this were recorded the history, demographic details, weight, height, and the results of tests for haemoglobin concentration and blood group. When indicated a general examination was done. Meanwhile, the secretary referred to a treatment allocation table, derived from random numbers, and extracted a box of tablets from one of the four categories; no attempt was made to stratify by age or sex. Instructions about dosage were given verbally by me and were also written on the box.

Whenever possible a urine specimen was obtained at the first consultation to act as a control and to exclude the possibility of self-medication with vitamins. The patient was asked to reattend weekly and to bring a specimen of urine to each consultation, a request which never seemed to arouse curiosity.

Prejudgement

The observer's bias should always be declared. My own, committed to paper before the trial began, was that imipramine probably had no specific action in depressive illnesses but might suppress anxiety and agitation by its sedative side-effect.

Rating Scales

Separate forms for each consultation were provided on which ratings were noted. A different form was used for each of the four consultations, and each time I remained ignorant —and usually forgetful—of the previous assessment. The rating scales were purposely kept simple, five traits being rated on five increments. The traits were: depression, anxiety, agitation, hypochondria, and retardation. The ratings were: absent (0), mild (1), moderate (2), marked (3), and severe (4). There is always a reluctance for those responsible for ratings to adopt an extreme score, and this tends to be rarely used. Two ratings higher than moderate were therefore deliberately introduced (marked and severe). If "severe" had been omitted it is probable that "marked" would have been rarely entered and the distributions would have tended to be negatively skewed; hence the use of an extra category opens out a distribution curve into a gussian shape.

After the last consultation the four completed forms were compared together for the first time, and the patient's progress was assessed; any change was measured by comparing the ratings for the first and last consultations. If necessary these were modified to take into account the intervening ratings and the results of a retrospective assessment, though few changes were in fact made. In addition to rating scales patients were also assessed according to their general state at the fourteenth and twenty-first days ("global assessment").

The initial ratings for each trait (Fig. 2) show that, except

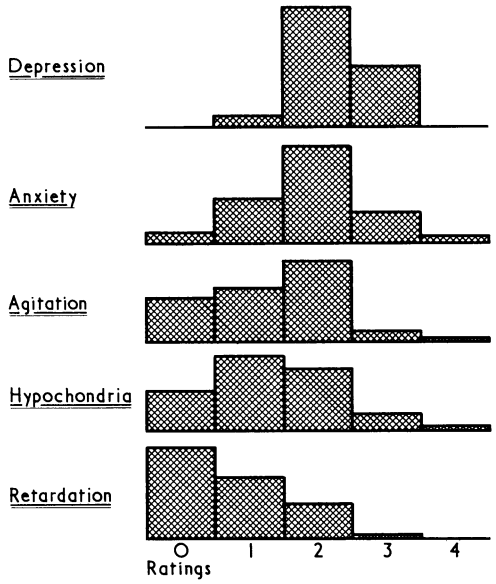

FIG. 2.—Distribution of ratings at entry for five traits.

for retardation, the mode for the different traits lies near the centre of the scale; retardation is rare in the type of case seen in general practice, and is not an important component of the illness. These distributions suggest that the traits and rating intervals were selected and used in a valid way.

Statistical Treatment

A psychiatric rating scale is intermediate to ordinal and interval scales; it has been argued that non-parametric computations should be applied exclusively to such behavioural data (Siegel, 1956). This view has been emphatically rejected by Lubin (1962) in a review of the problem, and it is now generally accepted that parametric tests may be legitimately applied to this type of material.

In this study the numbers of patients in each treatment group were unequal and thus the model was non-orthogonal; the change in ratings during the period of observation was therefore computed by a two-factor analysis of variance. This was done both for changes in the aggregate scores and also for changes in the separate traits.

There is a theoretical objection to basing an assessment on an analysis of absolute reduction in scores. Such an analysis assumes that a reduction in score from six to four involves a drug in as much "therapeutic effort" as a reduction from four to two. It may be argued, moreover, that a reduction of three on an initial score of nine is an improvement of 33%, whereas a reduction of three on six is a 50% improvement. Nevertheless, in this study the analyses of variance were not recal-

culated using percentage reduction instead of absolute reduction; both the number of increments in the scales and the range of movement of ratings within the scales were insufficient to make it necessary.

Results

Assessment data were available for 60 (the "contributors") out of the original 93 patients who presented with depression. It was possible to test whether these 60 were representative in respect of sex, age, marital status, and the incidence of previous depressive illness (Tables VII and VIII). The differences were found to be small and within the limits of sampling variation.

TABLE VII.—*Comparison of Traits for the Contributors and Non-Contributors*

	Sex		Marital Status		Past History of Depression	
	M.	F.	Married	Others	Present	Absent
Contributors ..	10	50	50	10	30	30
Non-contributors	6	27	28	5	18	15
Total ..	16	77	78	15	48	45
	$\chi^2=0.013$ P>0·9		$\chi^2=0.006$ P>0·9		$\chi^2=0.41$ P> 0·8	

TABLE VIII.—*Comparison of Age for the Contributors and the Non-Contributors*

	Age in Years			
	<35	35-54	55+	Total
Contributors*	25	26	9	60
Non-contributors†	12	15	6	33
Total	37	41	15	93

$\chi^2=0.31$; P>0·8.
*Mean age = 39·3 years. †Mean age = 40·8 years.

The "non-contributing" groups, however, included the patients with the more severe forms of depression, and in this respect the sample studied was unrepresentative of all depressive illness in the practice.

The 55 patients for whom complete data were available were allocated among the treatment groups as: placebo 14, placebo plus riboflavine 15, imipramine 13, imipramine plus riboflavine 13. Tests of the success of the allocation procedure in ensuring comparability of patients in the four treatment groups (Table IX) showed that the differences are small and within the limits of sampling variation.

TABLE IX.—*Comparison of Various Traits for Patients in the Four Treatment Groups*

	Sex. % of Females	Age in Years	Marital Status. % Married	Past History. % Present	Family Size. % with 1 or No Children
Placebo	88·2	39·7	82·0	47·0	53·0
Placebo plus riboflavine ..	86·7	41·3	80·0	47·0	47·0
Imipramine	85·7	37·1	100·0	57·0	57·0
Imipramine plus riboflavine ..	85·7	38·7	79·0	57·0	43·0
	$\chi^2=0.11$ P>0·7	$F=0.236$ $F_{0.05}=2.79$	$\chi^2=1.50$ P>0·2	$\chi^2=0.29$ P>0·5	$\chi^2=0.14$ P>0·7

Global Assessments

The number of patients judged to be recovered, improved, or unchanged at Day 14 are given in Table X; none was assessed as worse. There is no evidence that one treatment group did better than the others. A similar assessment at Day 21 also failed to show any difference between the treatment groups. Only 9 of the 60 patients (15%) did not show an improvement after three weeks.

TABLE X.—*Global Assessment at Day* 14

	Recovered or Improved	Unchanged	Total
Placebo	10	7	17
Placebo plus riboflavine	9	6	15
Imipramine	9	5	14
Imipramine plus riboflavine	9	5	14
Total	37	23	60

$\chi^2=0.18$; P=0·98.

Rating Scale Assessments

A two-factor analysis of variance was undertaken for the change in aggregate scores for the five traits (Table XI). The analysis of variance of the aggregate reduction in ratings shows that the sample is not homogeneous. Three observations may be made: (1) an assumption of no interaction between drugs (imipramine : riboflavine) is not contradicted; (2) an assumption that the addition of riboflavine to the placebo causes no difference is not contradicted; and (3) an assumption of no difference between the effects of placebo and imipramine may be rejected in favour of a superiority of placebo over imipramine.

TABLE XI.—*Analysis of Variance for Reduction in Aggregate Scores (n=55)*

	D.F.	Sum of Squares	Mean Sum of Squares	F
Variance due to effect of marking	1	1·09	1·09	N.S.
Variance due to effect of imipramine or placebo	1	34·2	34·2	4·22*
Interactions	1	0·009	0·009	N.S.
Residual	51	412·2	8·08	

*Significant at the 5% level.
D.F. = Degrees of freedom.

A two-factor analysis of variance was undertaken for the change in the separate scores of the five traits for each patient (Table XII). As in the aggregate assessments the significant and near-significant differences (hypochondria and agitation) are in the direction of favouring the placebo over imipramine.

TABLE XII.—*Analysis of Variance for Reduction in Scores of the Five Traits for each Patient (n=55)*

	D.F.	Sum of Squares	Mean Sum of Squares	F
Depression:				
Marked/unmarked	1	0·527	0·527	N.S.
Imipramine/placebo	1	0·743	0·743	N.S.
Interactions	1	0·022	0·022	N.S.
Residual	51	42·43	0·832	
Anxiety:				
Marked/unmarked	1	0·057	0·057	N.S.
Imipramine/placebo	1	1·065	1·065	N.S.
Interactions	1	1·269	1·269	N.S.
Residual	51	46·95	0·921	
Agitation:				
Marked/unmarked	1	0·000	0·000	N.S.
Imipramine/placebo	1	3·857	3·857	3·93†
Interactions	1	0·283	0·283	N.S.
Residual	51	50·04	0·981	
Hypochondria:				
Marked/unmarked	1	0·153	0·153	N.S.
Imipramine/placebo	1	3·618	3·618	4·592*
Interactions	1	0·505	0·505	N.S.
Residual	51	40·19	0·788	
Retardation:				
Marked/unmarked	1	0·229	0·229	N.S.
Imipramine/placebo	1	0·007	0·007	N.S.
Interactions	1	0·127	0·127	N.S.
Residual	51	27·162	0·533	

*Significant at 5% level. †Approaches conventional significance.

Discussion

The side-effects of imipramine ensure that no trial of this drug can be conducted under completely "blind" circumstances. In this study 15 patients complained of typical side-effects, and it was suspected that they were taking imipramine; the supposition was correct in 13 patients, who represented half of all those on the drug. This breach of the cipher is unfortunate and inevitable; its influence was perhaps reduced by the neutral attitude of the observer towards the effectiveness of the drug. The possibility of adding atropine to the placebo tablets was considered, but rejected as being undesirable.

The side-effects of imipramine had a further disadvantage; of the 19 overt defaulters 14 (74%) were taking imipramine rather than the placebo. This suggests that side-effects were an important cause for patients abandoning treatment.

The results of the survey and trial indicate that most depressive illnesses in general practice are of short duration and self-limiting but have a subsequent tendency to relapse. Almost all patients pass into a remission within three weeks of their first attendance, and there was no evidence that imipramine at the doses used was superior to a placebo in inducing such a remission; the side-effects of the drug did, however, prove to be troublesome. The superiority of placebo over imipramine, shown in two analyses, should probably be ignored; in this type of study one would prefer a smaller probability than the 5% recorded before accepting a deduction of superiority.

No interaction between imipramine and riboflavine was found; on this limited evidence it would seem not unreasonable to mark all tablets with riboflavine in a similar future trial. There was no evidence that the sedative effect of imipramine was useful in controlling the anxiety and agitation components of the illness.

Comparison of the results with those of previous trials is impracticable as this is the only trial to have been undertaken from a general practice; nevertheless its negative finding is consistent with the trend of other trials. Certainly the results of this trial cannot be transferred to hospital practice. It cannot be emphasized enough that the type of patient seen in a hospital outpatient department is selected and untypical of depression at large. This trial provides no evidence about the efficacy of imipramine in the severer forms of depressive illnesses. It does provide evidence to suggest that the milder forms of depression may be effectively treated with support and a placebo.

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REFERENCES

Abraham, H. C., Kanter, V. B., Rosen, I., and Standen, J. L. (1963). *British Journal of Psychiatry*, **109**, 286.

Agnew, P. C., *et al.* (1961). *American Journal of Psychiatry*, **118**, 160.

Ashby, W. R., and Collins, G. H. (1961). *Journal of Mental Science*, **107**, 547.

Ball, J. R. B., and Kiloh, L. G. (1959) *British Medical Journal*, **2**, 1052.

Bassa, D. M., and Vora, H. D. (1965). *American Journal of Psychiatry*, **121**, 1116.

Beck, A. T. (1967). *Depression*. New York, Hoeber.

Bodkin, N. J., Gaze, R. B., Gomez, G., Howlett, M. J., and Leigh, D. (1953). *British Medical Journal*, **2**, 723.

Bremer, J. (1951). *Acta Psychiatria et Neurologica (København)*, Suppl. No. 62.

Chiazze, L., Brayer, F. T., Macisco, J. J., Parker, M. P., and Duffy, B. J. (1968) *Journal of the American Medical Association*, **203**, 377.

Cooper, B., Brown, A. C., and Kalton, G. (1962). *Journal of the Royal College of General Practitioners*, **5**, 590.

Coppen, A. (1965). *British Journal of Psychiatry*, **111** 155.

Coppen, A., Shaw, D. M., Malleson, A., and Costain, R. (1966). *British Medical Journal*, **1**, 71.

Crombie, D. L. (1957). *College of General Practitioners. Research Newsletter*, **4**, 218.

Dalton, K. (1959). *British Medical Journal*, **1**, 148.

Daneman, E. A. (1961). *Diseases of the Nervous System*, **22**, 213.

Doust, J. W. L., Lewis, D. J., Miller, A., Sprott, D., and Wright, R. L. D. (1959). *Canadian Psychiatric Association Journal*, **4**, Suppl., S190.

Essen-Möller, E., and Hagnell, O. (1961). *Acta Psychiatrica Scandinavica*, **37**, Suppl. No. 162, p. 28.

Fluhmann, C. F. (1956). *The Management of Menstrual Disorders*, p. 104. London, Saunders.

Friedman, A. S., Granick, S., Cohen, H. W., and Cowitz, B. (1966). *Journal of Psychiatric Research*, **4**, 13.

Friedman, C., DeMowbray, M. S., and Hamilton, V. (1961). *Journal of Mental Science*, **107**, 948.

Fry, J. (1952). *British Medical Journal*, **2**, 249.

Fry, J. (1961). *Guy's Hospital Gazette*, **75**, 453.

Gunn, D. L., Jenkin, P. M., and Gunn, A. L. (1937). *Journal of Obstetrics and Gynaecology of the British Empire*, **44**, 839.

Hare, E. H., and Shaw, G. K. (1965). *Mental Health on a New Housing Estate*. London, Oxford University Press.

Helgason, T. (1961). *Acta Psychiatrica et Neurologica Scandinavica*, **37**, Suppl. No. 162, p. 81.

Höhn, R., Gross, G. M., Gross, M., and Lasagna, L. (1961). *Journal of Psychiatric Research*, **1**, 76.

Holdway, V. (1960). *Journal of Mental Science*, **106**, 1443.

Irvine, D. G., and Miyashita, H. (1965). *Canadian Medical Association Journal*, **92**, 551.

Juel-Neilsen, N., Bille, M., Flygenring, J., and Helgason, T. (1961). *Acta Psychiatrica Scandinavica*, **37**, Suppl. No. 162, p. 69.

Kenning, I. S., Richardson, N. L., and Tucker, F. G. (1960). *Canadian Psychiatric Association Journal*, **5**, 60.

Kessel, N., and Shepherd, M. (1962). *Journal of Mental Science*, **108**, 159.

Kessel, W. I. N. (1960). *British Journal of Preventive and Social Medicine*, **14**, **16.**

Lehmann, H. E., Cahn, C. H., and De Verteuil, R. L. (1958). *Canadian Psychiatric Association Journal*, **3**, 155.

Leigh, D. (1955). *Lancet*, **2**, 1285.

Leyberg, J. T., and Denmark, J. C. (1959). *Journal of Mental Science*, **105**, 1123.

Logan, W. P. D., and Cushion, A. A. (1958). *Morbidity Statistics from General Practice*, vol. 1 (general). London, H.M.S.O.

Lubin, A. (1962). *Annual Review of Psychology*, **13**, 358.

MacKinnon, A. U. (1966). *Practitioner*, **196**, 420.

MacKinnon, P. C. B., and MacKinnon, I. L. (1956). *British Medical Journal*, **1**, 555.

Manuila, A. (1958). *Journal of the American Medical Association*, **167**, 2047.

Masters, A. B. (1967). *British Journal of Psychiatry*, **113**, 1309.

Medical Research Council (1965). *British Medical Journal*, **1**, 881.

Miller, A., Baker, E. F. W., Lewis, D., and Jones, A. (1960). *Canadian Psychiatric Association Journal*, **5**, 150.

Noel, P. R. B. (1964). *Journal of the Royal College of General Practitioners*, **7**, 80.

Oltman, J. E., and Friedman, S. (1964). *Diseases of the Nervous System*, **25**, 699.

Overall, J. E. Hollister, L. E., Pokorny, A. D., Casey, J. F., and Katz, G. (1962) *Clinical Pharmacology and Therapeutics*, **3**, 16.

Parker, J. B., Theilie, A., and Spielberger, C. D. (1961). *Journal of Mental Science*, **107**, 936.

Paskind, H. A. (1930). *Archives of Neurology and Psychiatry*, **23**, 152.

Patch, I. C. L., Post, F., and Slater, P. (1965). *British Journal of Psychiatry*, **111**, 405.

Pedersen, A., Poort, R., and Schou, H. I. (1948). *Acta Psychiatrica et Neurologica*, **23**, 285.

Porter, A. M. W. (1966). *Practitioner*, **197**, 229.

Porter, A. M. W. (1968). *British Medical Journal*, **2**, 406.

Porter, A. M. W. (1969). *British Medical Journal*, **1**, 218.

Raphael, T., Searle, O. M., and Scholten, W. (1927). *American Journal of Psychiatry*, **7**, 153.

Rees, L., Brown, A. C., and Benaim, S. (1961). *Journal of Mental Science*, **107**, 552.

Richter, D. (1961). *Neuropsychopharmacology*, edited by E. Rothlin, vol. 2, p. 422. Amsterdam, Elsevier.

Riverius, L. (1661). *The Practice of Physick*, p. 353. London, P. Cole.

Robin, A. A., and Langley, G. E. (1964) *British Journal of Psychiatry*, **110**, 419.

Rothman, T., Grayson, H., and Ferguson, J. (1961). *Journal of Neuropsychiatry*, **2**, 158.

Roulet, N., Alvarez, R. R., Duffy, J. P., Lenkoski, L. D., and Bidder, T. G. (1962) *American Journal of Psychiatry*, **119**, 427.

Schorer, C. E., Lowinger, P., and Dobie, S. (1966). *Michigan Medicine*, **65**, 1071.

Shepherd, M., Cooper, B., Brown, A. C., and Kalton, G. (1966). *Psychiatric Illness in General Practice*. London, Oxford University Press.

Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*. New York, McGraw-Hill.

Silverman, C. (1968). *American Journal of Psychiatry*, **124**, 883.

Sloane, R. B., Habib, A., and Batt, U. E. (1959). *Canadian Medical Association Journal*, **80**, 540.

Sorensen, A., and Strömgren, E. (1961). *Acta Psychiatrica Scandinavica*, **37**, Suppl. No. 162, p. 62.

Taylor, Lord, and Chave, C. (1964). *Mental Health and Environment*. London, Longmans.

Watts, C. A. H. (1956). *British Medical Journal*, **1**, 1392.

Watts, C. A. H. (1966.) *Depressive Disorders in the Community*. Bristol, Wright.

Wittenborn, J. R., Plante, M., Burgess, F., and Maurer, H. (1962). *Journal of Nervous and Mental Disease*, **135**, 131.