From our experience in making this survey we support Burnet's (1953) suggestion for the establishment of permanent twin research departments in certain centres.

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"We are studying Irish males, who are between the ages of 30 and 60 years, have lived in the Boston area for 10 or more years, and who have a brother in Ireland who has never left the country. Preliminary results on about 200 Irishmen in Boston and 60 blood brothers in Ireland indicate that those who remain in Ireland consume an average of 300 calories more per day, and yet weigh less. This obviously means more physical activity—walking and bicycling in Ireland. Those who remain in Ireland consume more animal fats, with 94% of the total fat intake coming from animal fats including an average consumption of a pound of butter per week, and yet they have lower levels of serum cholesterol than their brothers in Boston—a mean value over the total age range of 206 mg./100 ml. versus 222 mg./100 ml. Hypertension is less than half as prevalent among the brothers as compared with brothers in Boston."—Stare, F. J., *J. Amer. med. Ass.*, 1961, **178**, 924.

TREATMENT OF ANXIETY STATES BY ANTIDEPRESSANT DRUGS

BY

WILLIAM SARGANT, M.B., F.R.C.P., D.P.M.

AND

PETER DALLY, M.B., M.R.C.P., D.P.M.

From the Department of Psychological Medicine, St. Thomas's Hospital, London

For nearly four years we have been experimenting with the use of the new antidepressant drugs in a variety of psychiatric conditions. As a result of an early trial of iproniazid with a selected group of depressed patients, who had been referred primarily for electric shock treatment, one of us (Dally, 1958) reported that iproniazid was useful in mild depressive states, but that sometimes it increased symptoms of chronic tension and anxiety in this particular group of depressions. Further experience with this drug and its more recently developed analogues, such as phenelzine, isocarboxazid, and the like, used on a much wider range of patients, led us to modify this view, and we then isolated and described a group of what we called "atypical" depressions—cases which seemed particularly responsive to the monoamine-oxidase inhibitors (M.A.O.I.) (West and Dally, 1959; Sargant, 1960, 1961). This group included cases showing both hysterical and phobic anxiety symptoms, and sometimes the illness more closely resembled an anxiety hysteria or a reactive depression than a true endogenous depression. Since then we have come increasingly to recognize that these atypical depressions do overlap with, and are sometimes indistinguishable from, illnesses which many clinicans would very often label as anxiety neuroses.

Pure anxiety states are rarely seen in clinical practice because secondary symptoms of hysteria, depression, or obsessional thinking generally complicate the picture, especially when the illness has persisted for any length of time. Anxiety states have also generally been much more difficult to treat in a simple and satisfactory manner than have true depressions. It therefore seems of great importance from a therapeutic point of view to find now that M.A.O.I. used alone, or combined with chlordiazepoxide hydrochloride ("librium"), can often be very effective in the treatment of certain anxiety states, even where there may be no obvious sign of depression. Though the literature has in the past contained isolated references to the value of M.A.O.I. in states of anxiety and tension (Dickel *et al.*, 1959; Gallinek, 1959), yet with the intensive work and advertising of these drugs for the depressive states their value in the former group of patients has mostly been overlooked by psychiatrists and general physicians alike.

To illustrate these points we report the effect of M.A.O.I. drugs on 60 out-patients with neuroses, who had previously been diagnosed and treated as "atypical" or reactive depressions, anxiety hysterias, or anxiety neuroses. Such diagnoses, as we have suggested, often overlap each other. Fortunately, these patients were mostly well known to us, and had been attending the department for considerable periods of time. All the patients were first given a combination of M.A.O.I. and chlordiazepoxide. Subsequently the effect of giving each drug alone was tried. It was most important to find

that in all the patients who had made a good response to this combination a return of symptoms quickly followed when the M.A.O.I. was withdrawn and the patient was left on chlordiazepoxide alone.

The M.A.O.I. used in these patients were phenelzine, isocarboxazid, phenoxypropazine, and, in six cases, iproniazid. The doses of phenelzine were 40–60 mg., of isocarboxazid 30–40 mg., of phenoxypropazine 20–25 mg., and of iproniazid 100–150 mg. a day. The amount of chlordiazepoxide given ranged from 20 to 60 mg. a day.

Results

Three main groups of patients could be differentiated on the basis of their response to these drugs (Table I). The first group was found to respond to the M.A.O.I. alone, the second responded best to a combination of M.A.O.I. and chlordiazepoxide, and the third failed to respond or were made worse by M.A.O.I., although this last group did respond in some measure to the use of chlordiazepoxide alone. The three groups were similar in respect of age and sex, but in the third group symptoms had mostly been present longer than in those of the other two groups.

TABLE I

	Group 1, Responding to M.A.O.I. Alone	Group 2, Responding to M.A.O.I.+ Chlordiazepoxide	Group 3, Not Responding to M.A.O.I.+ Chlordiazepoxide
No. of cases ..	15 (12 F., 3 M.)	28 (18 F., 10 M.)	17 (11 F, 6 M.)
Average age ..	41 years	42 years	41 years
Average length of illness	5 ,,	5 ,,	7 ,,
Positive family history	47% (7)	32% (9)	23% (4)
Past breakdowns ..	53% (8)	44% (12)	53% (9)
Good previous personality	87% (13)	75% (21)	29% (5)
Precipitating factors	73% (11)	46% (13)	23% (4)
Anxiety present:			
Diffuse	100% (15)	75% (21)	70% (12)
Phobic	0	25% (7)	30% (5)
Hysterical behaviour	27% (4)	43% (12)	23% (4)
Depression present:			
Marked ..	13% (2)	3% (1)	0
Mild	87% (13)	97% (27)	94% (16)
Blame, self ..	27% (4)	14% (4)	0
,, others ..	13% (2)	32% (9)	65% (11)
Worse (a.m.) ..	60% (9)	36% (10)	6% (1)
Weight loss 7 lb. (2.7 kg.) ..	47% (7)	40% (11)	12% (2)

Number of patients are given in parentheses.

Group 1

Group 1 patients, responding to M.A.O.I. alone, showed some obvious depressive symptoms, had good basic personalities (in terms of work record, marriage stability, etc.) and relatively stable autonomic systems, and had broken down only after severe or prolonged stress. The following is a good example.

A farmer's wife aged 42 gave a four-year history of headache and generalized pains in the face and abdomen. All her front teeth had been removed without effect. She had a constant feeling of anxiety, and bouts of weeping and depression. She felt exhausted, was emotionally labile, and was able to carry on working only by an effort of will. Symptoms tended to be worse in the morning and late at night. She had difficulty in getting to sleep and then woke frequently. Sexual feelings were lost, appetite was poor, and she was half a stone (2.7 kg.) under her usual weight. No organic cause for these symptoms was found on repeated examinations. She was treated with a variety of sedatives and tranquillizers without effect, and subsequently had psychotherapy for six months. Previously she had been a conscientious, cheerful, lively woman, who had looked after her family well and helped her husband in his work. Her husband was a heavy drinker, more interested in his farm than in his wife. The sexual side of the marriage had never been satisfactory, but she had adjusted to this until just before her symptoms began. At this time she had been seduced by an employee of her husband's. The arousal of satisfying sexual feelings for the first time conflicted with the sense of guilt she felt for what had occurred. Psychotherapy enabled her to break off the affair, but failed to diminish her symptoms of severe anxiety. Electric shock only increased her tension, but iproniazid, and later phenoxypropazine, rapidly caused the symptoms to abate.

Group 2

Group 2 patients, responding best to M.A.O.I. and chlordiazepoxide combined, but not to the latter alone, seemed to be less stable in their autonomic responses. Anxiety was the most prominent symptom present, and there was often phobic, hysterical, or obsessive colouring to the total picture. It is this group that so many people might label as anxiety states or anxiety hysteria. Two examples follow.

A woman of 36 was referred with a history of recurring phobic anxiety after an attempted sexual assault at the age of 17. She was afraid to go out alone and became claustrophobic when travelling on a train or bus. She was a determined, conscientious woman, and at first was able to force herself to go out in spite of her fears. Her symptoms improved after marriage at 21 years, and almost disappeared during pregnancy. But at the age of 30 the phobias began to increase, and eventually became so bad that she was unable to go out alone. She became tense and irritable, and was constantly quarrelling with her husband, which increased her anxiety still more. She had had analysis and hypnosis without benefit, and only barbiturates and meprobamate gave her any relief at all. She was given isocarboxazid and chlordiazepoxide, and three weeks later reported that she had been out alone in a bus for the first time in three years. For the past 15 months she has been almost free of symptoms, but any attempt to stop either of the drugs leads to a relapse.

A man of 56 was referred from the medical out-patient department in a state of acute anxiety. He was a "highly strung," obsessive business man. He had had no previous breakdown, but four months earlier thyrotoxicosis had been diagnosed and treated satisfactorily with radioactive iodine. He had felt tired and irritable after that, had difficulty in sleeping, and had lost most of his libido. His weight had increased by a stone (5.4 kg.). He was happily married, and had no serious problems at this time, but he was constitutionally prone to worry about something. On the day he was seen, while in the street, he was brought to a halt by a sense of constriction in the chest and a feeling of panic. His heart was racing and thumping; he was shivering with cold and sweating profusely, and was unable to stand without support. He feared he was about to die, and this fear was still with him when he was brought to hospital. Coronary disease was excluded, and he responded rapidly and fully to isocarboxazid and chlordiazepoxide. Attacks of panic recurred when isocarboxazid was withdrawn, but stopped when it was given again.

Group 3

Group 3 patients, most of whom suffered predominantly from chronic anxiety and tension states, did not do well with M.A.O.I. and chlordiazepoxide, and had responded best in the past to short-acting barbiturates (Table II). The main difference was that

TABLE II.—*Response (Partial) to Drugs Other Than M.A.O.I.*

Drug	Group 1	Group 2	Group 3
Barbiturates (short-acting) ..	0	21%	91%
Chlordiazepoxide	0	61%	64%
"Drinamyl"	85%	86%	82%

their personalities were usually not as good as those of the first two groups. The following is a typical instance of this.

A woman of 36 became "strung-up" after her marriage at the age of 18, and was worse after the birth of her two children. This "strung-up" feeling increased at the time of her periods, and during episodic exacerbations she was afraid to go out alone. She felt tired and depressed, and on one occasion, after a quarrel with her husband, took an overdose of chloral hydrate. At times she was unable to swallow because of tightness of the throat; at other times she sweated, "trembled all over," and felt sick and giddy. She had difficulty in getting to sleep without a sedative. She came from an unhappy home and had married her husband mainly in order to escape from this. After marriage she gradually developed a loathing for intercourse, and tried to avoid it by every possible means—a situation which led to considerable tension at home. Psychotherapy failed to make any impression on her symptoms, and only large doses of amylobarbitone gave her any relief. M.A.O.I. seemed to increase her anxiety, but chlordiazepoxide alone did help her, although not as much as the barbiturates did.

Correct Dosage of Drugs and Timing

Iproniazid still remains the most effective M.A.O.I. in the treatment of both "atypical" depressions and anxiety states, but owing to its somewhat toxic effects on the liver it should only be used exceptionally when other drugs have failed to help the patient. Some patients respond better to one M.A.O.I. than to another, sometimes owing to differences in side-effects. Patients must be warned that no improvement may be felt for four to eight days after the beginning of treatment, and that full doses must be taken for at least 10 days before deciding that they are likely to be without effect. It is also most important to regulate the dosage of the drugs given, so that side-effects such as fainting and giddiness do not mask the beneficial ones. Thus in those of large body-build phenelzine 15 mg. q.d.s. or isocarboxazid 10 mg. q.d.s. and chlordiazepoxide 10 mg. t.d.s. are good starting doses; smaller doses, such as phenelzine three times a day and chlordiazepoxide twice a day, were used for the others.

The dose of M.A.O.I. should be lowered if faintness or giddiness becomes prominent, but too great a drop in dosage may result in loss of effectiveness. Subsequently, relatively small doses of the drugs may be all that are required to maintain the improvement obtained. In recent anxiety states the drugs may be stopped after a month or two, but some patients seem to need maintenance doses for a considerable time, and so far no serious harm has come from their use over long periods. However, occasional cases of jaundice are now starting to be reported with all the M.A.O.I. drugs as well as with iproniazid. If improvement is followed by relapse when the drug has been withdrawn, it can always be started again in full dosage, returning as quickly as possible to a maintenance dosage for as long as necessary.

Discussion

This combination of the M.A.O.I. and chlordiazepoxide has been found by us in large numbers of cases to be the most effective treatment at present available for anxiety states occurring in patients with *good previous personality*. Some form of psychotherapy is sometimes needed in addition, but it is remarkable how much these drugs have reduced the need for more intensive forms of psychotherapy in many of these patients. Some have had their symptoms for years and have not been helped by any previous treatments, except perhaps the short-acting barbiturates; even after several years of incapacity some of those with long-standing phobic states have, most surprisingly, been able to resume a normal life. Patients with cardiac neurosis or effort syndrome, hitherto a most difficult group to help in any way, have responded particularly well. Palpitation, hyperventilation, flushing, sweating, and pain over the heart may convince these patients that they have heart disease, and this leads to a vicious spiral of mounting anxiety and autonomic overactivity. Even when true angina is present, anxiety may increase the symptoms out of all proportion and lead on to total disablement. Treatment with M.A.O.I. and chlordiazepoxide will generally lead to a marked improvement within a week or 10 days in such patients, especially when their previous personalities have been good and the illness has been of recent onset. We regard this treatment as a most significant advance on any other method in a hitherto very difficult group of patients.

Many of the patients with anxiety states who respond to these drugs have formerly been driving, capable people, sometimes occupying positions of responsibility. Often they have been wary of taking purely sedative and habit-forming drugs, such as the barbiturates. They have tried to carry on in spite of disabling symptoms, and have broken down only after great stress (Table I). Anxiety is, however, always much nearer the surface in persons with less stable previous personalities, and this tends to have much more disruptive effects on their lives. Consequently, such patients are constantly breaking down and finding themselves unable to cope with their responsibilities. M.A.O.I. do not generally help anxiety states seen in chronically inadequate personalities, and sometimes may even increase anxiety and obsessive rumination, as reported in an earlier paper (Dally, 1958).

The question must now arise whether M.A.O.I. are really the antidepressant drugs they are claimed to be, or whether they really act more against anxiety, and perhaps as stabilizers of the autonomic nervous system. Such a question inevitably brings up the controversial problem of what is meant by the terms "depression" and "anxiety." Lewis (1934) believes that it is impossible to separate clinically groups of depressions one from the other; he regards anxiety often as a symptom of depression, and anxiety states and depression as forming one long continuum of illnesses. Garmany (1958) only distinguishes mild, and therefore more reactive, depression from severer forms of depression. Walker (1959) has even concluded that most anxiety states that recover are really cases of depressive illness. Others, however, have emphasized the differences rather than the similarities between these groups of patients, and discussion and disagreement still goes on (Partridge, 1949).

In the present state of our knowledge it seems unproductive to argue too much about these differences of opinion. But it must be accepted that endogenous, reactive, or atypical depressions and anxiety states do overlap and cannot always be distinguished with certainty. It may be that there is no basic distinction between them, and only a difference in underlying personality structure and a greater or less degree of reactivity.

None the less, we believe that it is important for therapeutic purposes to continue to try to distinguish the symptomatology of certain subgroups among the

affective disorders. We have found, for instance, that those patients with anxiety states or depressions most likely to respond to M.A.O.I., or to M.A.O.I. combined with chlordiazepoxide, do generally have certain characteristics in common. Early-morning waking may be present, but more often there is an inability to get to sleep, or there may even be an increased depth of sleep. Many patients also tend to get worse as the day goes on rather than better, which is very different from the constant early-morning waking and diurnal mood-swing of the true endogenous depression. Severe fatigue is a common complaint, and there is a great variation in the patient's symptoms and in his emotionality from day to day. Patients also tend to blame others rather than themselves, and premenstrual tension and irritability are very commonly found in the symptomatology of women who are going to make a good response to the M.A.O.I. drugs.

After four years' experience of a wide range of antidepressant drugs, we have found M.A.O.I. to act best in these anxiety and atypical depressive states, rather than in the more typical endogenous depressive illnesses, which generally do better with imipramine combined with electric convulsion treatment. In fact, it seems that if an anxiety state or an "atypical" depression, particularly of recent origin and occurring in a patient of good previous personality, does not respond within 10 days to one or other of the M.A.O.I. drugs and chlordiazepoxide, correctly given, both the diagnosis and the treatment should be reconsidered. Then, especially in the middle-aged, it will often be found that anxiety symptoms are masking a deep underlying depression needing additional or other treatment.

Summary

Two years ago iproniazid was reported as being valuable in the treatment of "atypical" depressions. Subsequent experience with iproniazid and the newer monoamine oxidase inhibitors (M.A.O.I.) has shown that there is no clear treatment demarcation between some atypical depressions and anxiety states; and many anxiety states have now, in fact, been found to respond equally well to treatment with the M.A.O.I., preferably combined with chlordiazepoxide hydrochloride.

To illustrate these points, the effect of these drugs on 60 out-patients with a diagnosis of atypical depression, anxiety hysteria, or anxiety neurosis is reported. They fall into three groups: 15 patients responded to M.A.O.I. alone, 28 did best with M.A.O.I. combined with chlordiazepoxide, and 17 did not respond to M.A.O.I. Chlordiazepoxide given alone to these patients was much less effective, except in the last group.

These findings are discussed, and stress is laid on the proper use of M.A.O.I. drugs to avoid undesirable side-effects and relapse. The essential factor for success with M.A.O.I. and chlordiazepoxide in the treatment of anxiety states is a good previous personality.

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PHENELZINE AND DEXAMPHETAMINE IN DEPRESSIVE ILLNESS

A COMPARATIVE TRIAL

BY

E. H. HARE, M.D., D.P.M.
Physician

J. DOMINIAN, M.B., M.R.C.P.Ed.
Registrar

AND

L. SHARPE, M.B., D.P.M.
Registrar

Bethlem Royal and the Maudsley Hospitals, London

The basic cost to the National Health Service of a week's treatment with three common antidepressive drugs is as follows: imipramine, 50 mg. t.i.d., about 11s. 6d.; phenelzine, 15 mg. t.i.d., about 5s.; dexamphetamine sulphate, 5 mg. b.d., 1d.* Yet, so far as we can determine, there appears to be only one report in which the efficacy of one of the more expensive of these drugs has been compared with that of the cheapest by a controlled trial. Doust *et al.* (1959) compared imipramine and dexamphetamine in 24 depressed patients and found neither drug to be significantly better than a placebo.

In the present paper we report a controlled comparative trial of phenelzine, dexamphetamine sulphate, and lactose (as placebo) in the treatment of depressive illness of moderate severity. Apart from the paper by Doust *et al.* (1959), we have not found any report of a controlled trial of dexamphetamine sulphate in depression. There have been a number of controlled trials of phenelzine, but the results are conflicting: thus Rees and Davies (1961) found it of value, but Harris and Robin (1960) and Keith (1959) did not.

There is at present no means of measuring the clinical state of a depressed patient except by the subjective judgment of the clinician. This circumstance does not, of course, impugn the validity of an adequately controlled trial, but the results of such a trial might nevertheless be more convincing if it were shown that the clinical assessments were reasonably reliable—that is, that there was a consistency between the assessments of different clinicians at any one time. In the present trial we have attempted to measure the reliability of our assessments.

Method

Selection for the Trial.—The trial was restricted to patients who were diagnosed as having a primary depressive illness, who did not have symptoms associated with schizophrenia or organic brain disorder, who had not received electric convulsion therapy during the previous three months, and who had had no antidepressive drug treatment during the previous two weeks. No distinction between endogenous and reactive types of depression was attempted.

Subjects.—Forty-six patients entered the trial but three failed to complete it (one left hospital against advice,

*Basic N.H.S. prices in May, 1961, were: "tofranil" (imipramine), 25-mg. tablets, 1,000 for 275s.; "nardil" (phenelzine), 15-mg. tablets, 500 for 97s. 10d. plus 24s. 5d. purchase tax; dexamphetamine sulphate, 5-mg. tablets, 1,000 for 6s.