Brit. J. Psychiat. (1977), 130, 432–51

Review Article

The Practical Management of Affective Disorders

By DAVID M. SHAW

Introduction

The affective disorders vary in severity from mild but nevertheless distressing self-limiting alterations in mood, many of which never come to medical attention, right through to the most severe and disabling psychotic states. This article has been confined to the management of those episodes which are referred to the psychiatrist, usually because of the severity of the illness or the fact that treatment by the general practitioner has failed.

It is an appropriate time for a discussion of the problems associated with the treatment of affective disorders, but the present state of current research necessarily implies that present decisions on management will be based on data which may be superseded in the near future by new information and ideas.

Despite an enormous amount of detailed work on the treatment of depression, much remains to be done. The impact of life events on cyclothymia and on episodes of affective illness rather than, for instance, on the symptom of depression could be explored further. It would be of interest to examine the relationship between life-styles and frequency of episodes, and the suitability of various milieux for promoting the most rapid recovery. There is an urgent need for the monitoring of antidepressant medication and for information on whether or not therapeutic levels have been achieved. If this facility were available it would be much easier to define those patients within the term affective disorder most suitable for a particular treatment. Meanwhile, new families of potential antidepressants have appeared whose efficacies and degrees of overlap with established remedies and other characteristics await clarification. Ability to assess the achievement of different levels of antidepressant drugs might help to unravel the problem of patients with resistant depression. Differences in rate and type of metabolic degradation of antidepressants, metabolic changes within individuals produced by continuous therapy, drug interactions and long-term effects of various kinds may also repay further studies.

Aspects of the Pharmacology of Drugs used for Affective Illness

(1) Tricyclic antidepressants

The important metabolic step in the degradation of tricyclic antidepressants is oxidation in the liver (Glassman, 1973). This process, dosage and body mass, are the main determinants of the steady state levels of the drugs achieved in the body. The enzyme system involved in the liver is shared by many drugs (Dayton and Perel, 1971; Kato, Chiesara and Vassanelli, 1963; Shand and Oates, 1971; Bellward and Morgan, 1972). Thus, if chlorpromazine (or one of a number of other drugs) is given with a tricyclic antidepressant, 'enzyme inhibition' may occur, that is, the two tend to compete for the available enzyme and 'share it' between them. As a result, there will be a slower rate of destruction of the tricyclic compound (Gram and Overø, 1972). A further complication is that the compounds sharing the degrading hepatic enzyme system may induce the production of more enzyme (Lader, 1976; MacDonald and Robinson, 1968; O'Malley, Browning, Stevenson and Turnbull, 1973; Cucinell, Conney, Sansur and Burns, 1965). If, for instance, a tricyclic antidepressant is given with chlorpromazine over a period of time,

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

extra hepatic enzyme will be produced. Whether or not the coexistence of 'enzyme inhibition' and of a larger pool of enzyme results in higher or lower tricyclic levels in the body depends on which predominates. With chlorpromazine it is probably enzyme inhibition, so that tricyclic levels are raised (Gram and Overø, 1972).

There could be advantages and disadvantages to these interactions. Starting a tricyclic with a 'competing' drug could give unusually high levels of the former, unpleasant early side effects, and rejection of the drug by the patient; but in others it might bring an ineffective level of tricyclic antidepressant up to the therapeutic range. Discontinuing the additional compound later might cause a marked fall in tricyclic levels by removing competition for degradation after inducing an increased pool of the enzyme, which, however, would fall later to normal levels.

On the whole, polypharmacy of this kind has the disadvantage of confusing matters in therapy with tricyclic drugs, and therefore should be avoided if possible. When it cannot be avoided with a tricyclic antidepressant, it is worth remembering that an additional drug may affect the tricyclic at the time when the additional compound is added, during therapy and when it is discontinued, and this is quite apart from any pharmacological interactions. On the credit side, however, is the fact that there have been attempts to use competition to improve treatment with tricyclics (Wharton, Perel, Dayton and Malitz, 1971; Flemenbaum, 1971).

The magnitudes of the changes discussed above are of importance in the management of the treatment of individuals. It must be stressed, however, that they are relatively small compared with genetically determined differences between individuals in the way they metabolize drugs. This is illustrated by the fact that a fixed daily dose of a tricyclic antidepressant produces wide variations in plasma levels, e.g. a range of 48 to 238 ng/ml from 150 mg nortriptyline (Kragh-Sørensen, Åsberg and Eggert-Hansen, 1973). Tertiary amine tricyclic antidepressants, e.g. amitriptyline and imipramine, are converted to their secondary amine derivatives, e.g. nortriptyline and desipramine respectively (Crammer, Scott and Rolfe, 1969) which may be present in different individuals in a wide range of concentrations relative to the parent compound (Braithwaite, Goulding, Theano, Bailey and Coppen, 1972; Gram, Reisby, Ibsen, Nagy, Dencker, Beck, Petersen and Christiansen, 1976). In addition, it is likely that the proportions between tertiary amine drug and its secondary amine product vary considerably in the individual from hour to hour with the distance in time from the previous dosage, the method of spacing dosages, etc. (Hullin, 1976, personal communication).

(a) *Plasma levels and response to treatment*

Understanding what may be going on in an individual's response to treatment with a tricyclic drug is complicated by the fact that we do not know enough about the relationship between the plasma level and the therapeutic response. Åsberg, Crönholm, Sjöqvist and Tuck (1971) have suggested that the plasma level response curve for a secondary amine tricyclic, nortriptyline, is in an inverted U, low and high dosages tending to give inferior results. Kragh-Sørensen, Åsberg and Eggert-Hansen (1973) found that levels of nortriptyline above 170 ng/ml were associated with poor therapeutic response, which in a proportion of a small group was remedied by reducing the input of the drug. Similarly, Whyte, MacDonald, Naylor and Moody (1976) found that protriptyline was most effective at plasma levels within a median range of 630–900 nM/L.

In contrast, with a tertiary amine tricyclic antidepressant, amitriptyline, when amounts of tertiary amine parent substance and secondary amine derivative were summed, 120 ng/ml gave little therapeutic benefit; but above this there was no indication of an 'upper limit' (Braithwaite, Goulding, Theano, Bailey and Coppen, 1972), that is, response tended to improve as plasma level increased, without an apparent ceiling. Gram *et al* (1976), using imipramine, found minimum levels of imipramine and desipramine for clinical response and no real evidence of an upper limit.

Pending the possession of more knowledge on tricyclic drugs, it must be assumed that amitriptyline and imipramine and possibly other

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

tertiary amine tricyclics (such as clomipramine, trimipramine, doxepin, dothiepin, dibenzepin) will be much easier to use than secondary amine tricyclics (such as nortriptyline, desimipramine, protriptyline). This is because response to therapy with amitriptyline and imipramine appears to improve with increasing dosage, which therefore can be pushed to the point of tolerance in the hope of producing a better outcome if the patient is not responding on a lower dose. On the other hand, failure to recover whilst taking nortriptyline or protriptyline could be because the drug is being given in either too large or too small amounts. Of course, extrapolation from these data to the other class members may not be justified, and the findings need to be extended. The situation would be much simpler for the clinician if there were a close relationship between side effects and optimum dosage. This has been claimed for nortriptyline by Åsberg, Crönholm, Sjöqvist and Tuck (1970), but not found in a study of amitriptyline by Braithwaite *et al* (1972).

(b) *Other interactions of tricyclic antidepressants*

Some hypotensive drugs—guanethidine, bethanidine and debrisoquine—are taken up into adrenergic neurones before exerting their hypotensive actions. Tricyclic drugs may block this process, preventing the hypotensive drugs from reaching their site of action; so tricyclic antidepressants should not be given to patients on these drugs.

Tricyclic antidepressants have atropine-like actions, and these can be synergistic with other anticholinergic compounds, to produce unpleasant and potentially harmful effects, including glaucoma, paralytic ileus and urinary retention.

(2) **Monoamine oxidase inhibitors (MAOI)**

Amines such as 5-hydroxytryptamine, noradrenaline, adrenaline, histamine, dopamine, etc, may be metabolized by a group of enzymes known as monoamine oxidases. These enzymes have important functions, which include:

(i) being part of a complex system regulating the levels of transmitter amines in aminergic neurones; and

(ii) preventing the passage of amines from the gastrointestinal tract into the circulation. When monoamine oxidases are blocked, the protection afforded by (ii) above is lost.

Tyramine seems to be the most widespread potentially harmful amine in foodstuffs. It is an indirect sympathomimetic amine, that is, it exerts its effects not by a direct action on adrenergic receptors, but by provoking release of catecholamines, leading to hypertension and sometimes to hyperpyrexia.

Inhibition of monoamine oxidase leads to 'loss of protection' in other respects. Indirect sympathomimetic compounds other than tyramine or substances which give rise to derivatives with such characteristics can become hazardous. Other medicaments interact with MAOI in ways which are not yet fully understood.

Most of the data in this and the following sections on MAOIs are to be found in review articles by Boakes (1971 and 1974), Massey Stewart (1976) and Stockley (1974), so details of references to some of the original work have been omitted.

(a) *Interactions of MAOI with foods*

When monoamine oxidases are inhibited, 5–7 mg of tyramine may cause an increase in blood pressure, and 25 mg can precipitate a hypertensive crisis. The foodstuffs which in average portions contain tyramine in excess of this latter amount are mature cheeses (up to 100 mg) and pickled herrings (up to 75 mg). Yeast and meat extracts such as Marmite and Bovril contain up to 2 mg/gram, and drinks or stews containing these products could give significant levels of tyramine.

Chianti contains up to 7·5 mg in 300 ml, and beer up to 10 mg in a litre. Sherry contains some tyramine, but spirits, being distilled, should be free of this compound.

Game and badly stored meat, offal, pâtés, fish or any protein food which is not fresh must be regarded with suspicion because of the possible presence of tyramine produced by bacteria. Banana *skins* and broad bean *pods* must be avoided, the latter because they contain dopa, but neither is commonly used in European dishes.

A suggested instruction sheet for the patient

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

is given in Appendix 1, and includes a warning concerned with interactions with medicines.

(b) *Interactions of MAOI with drugs*

(i) *Tyramine-like drugs*

The following drugs with tyramine-like actions (or giving rise to a product with sympathomimetic activity) are contraindicated:

(a) amphetamine, mephentermine and other pressor agents;

(b) ephedrine, phenylephrine (and other similar nasal decongestants);

(c) phenylpropanolamine (proprietary cough and cold cures);

(d) fenfluramine, phenmetrazine, chlorphentermine and other amphetamine-like anti-obesity agents;

(e) levodopa (antiparkinsonian therapy).

(The use of noradrenaline and adrenaline is relatively safe.)

(ii) *Tricyclic antidepressants*

There is considerable controversy about the use of MAOI with tricyclic antidepressants, because they can interact together, particularly if the tricyclic is introduced when the patient is already taking MAOI (Sethna, 1974). The use of combined MAOI and tricyclic compounds has been discussed by Schuckit, Robins and Feighner (1971), Sethna (1974) and Lipsedge (1976). The combinations normally used are amitriptyline or trimipramine for the tricyclic drug, and isocarboxazid, phenelzine or tranylcypromine for the MAOI; and other 'experimental' combinations are not recommended. The patient has to be free from MAOI and tricyclic drugs for one week before starting combined drug therapy and must observe the usual MAOI dietary and drug precautions. In addition, the drugs should be started and continued together from the very beginning (*Lancet*, 1965; Sethna, 1974), and if there is a lapse in the taking of one or other during the course it may not be safe to reintroduce the second drug. It is preferable to leave combined antidepressant therapy to specialized centres.

(iii) *MAOI with MAOI*

If, for any reason, there is a need to change from one MAOI to another, a gap of a week should be allowed between them, because, although this is poorly documented, there is some evidence that dangerous interactions may occur.

(iv) *Miscellaneous compounds*

(a) Pethidine can interact with MAOI to give serious side effects. The reasons for this are not known as yet, and it only applies to some susceptible individuals. Morphine is a safer compound for patients on MAOI.

(b) α-methyldopa and reserpine should be used with caution in patients who are established on MAOI, because animal experiments suggest that they could produce central excitation. The effect of other antihypertensive drugs may be enhanced.

(c) The effects of hypoglycaemic agents is increased, so that the giving of MAOIs to a diabetic must be closely supervised, with appropriate readjustment of dosage to prevent exaggerated falls in blood glucose.

(d) The actions of barbiturates, chloral hydrate and possibly alcohol may be prolonged.

(e) There are indications that antiparkinsonian drugs may interact with MAOI in animals (Pedersen and Møller Neilsen, 1975), but the clinical importance of these observations is not yet known.

[*Treatment of toxic reactions*. Toxic reactions with MAOI fortunately are uncommon and the most common are self-limiting tyramine hypertensive episodes. This very rarity of MAOI interaction means that most psychiatric registrars have no experience of dealing with them, and an instruction sheet similar to that in Appendix 2 should be available.]

(c) *Metabolism of MAOI*

Phenelzine is probably inactivated by acetylation (Rawlins, 1974), but this is not established beyond doubt (Marshall, 1976). However, clinical response, at least in neurotic depressives, seems to be related to acetylator status (Johnstone, 1974). The gene for slow acetylation is recessive to rapid acetylation (Price, 1967). The percentage prevalence of rapid acetylators is different in different populations, being about

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

46 per cent in the U.K. (Rawlins, 1974). Ability to acetylate rapidly is important because, if this is the route for metabolism of, say, phenelzine, with nearly half the population, the drug is likely to be metabolized rapidly, and therapeutic levels may be difficult to achieve in these individuals. When the route of metabolism is determined it should be possible to make a further assessment of phenelzine, taking account of acetylator status or perhaps measuring drug levels in plasma when techniques become available (Johnstone, 1974), or assessing the degree of MAOI inhibition.

In the meantime it may be that much greater flexibility in the dosage of all MAOIs is needed, but in particular when using phenelzine.

(3) Tryptophan

A number of workers have reported a potentiating effect of trytophan on the recovery of patients treated with MAOI (Coppen, Shaw and Farrell, 1963; Pare, 1963; Coppen, Shaw, Herzberg and Maggs, 1967; Glassman and Platman, 1969; Ayuso Gutiérrez and López-Ibor Aliño, 1971), but tryptophan by itself has produced variable results (Coppen, Shaw, Herzberg and Maggs, 1967; Broadhurst, 1970; Coppen, Prange, Whybrow, Noguera and Maggs, 1972; Carroll, Mowbray and Davies, 1970; Dunner and Goodwin, 1972; Herrington, Bruce, Johnstone and Lader, 1974 and 1976; and others). Tryptophan has little in the way of side effects, and has produced no toxic interactions with other drugs.

(4) Relative hazards of antidepressant drugs and from the illness

In Table I are data on some of the drugs used in affective illness, abstracted from the paper of Girdwood (1974) which gives reported deaths per 1,000,000 prescriptions. The values given for deaths per 1,000,000 *illnesses* could be obtained only if the average number of prescriptions per illness were known.

TABLE I

Ratio of reports per annum of deaths/millions of prescriptions

Amitriptyline	2·3
Imipramine	3·6
Chlorpromazine	8·6
Tranylcypromine	13·7
Phenelzine	17·2

[Taken from Girdwood, 1974]

There are two reasons why the figures for tricyclic antidepressants may underestimate the hazards from these drugs. Tricyclic compounds are prescribed by many doctors for long periods at relatively low dosage, so that the deaths per 1,000,000 prescriptions will represent a smaller population at risk than the corresponding figure for MAOI. In addition, Davidson (1976) gave doses of tricyclic antidepressants equivalent to normal therapeutic amounts in humans to dogs with ECG abnormalities. They remained well if not subjected to stress, but if this happened the majority died suddenly, and this also occurred in animals given artificial cardiac lesions by ligation of coronary arteries. Davidson (1976) studied sudden death in men experiencing cold or exercise stress at the time of the first fall of snow at the beginning of the Canadian winter, and for every death in an individual not on drugs there were eight in persons who had been taking tricyclic drugs. This is a most alarming finding and suggests that the triad of cardiac disease, tricyclic antidepressants and stress is particularly hazardous. It is likely also that many cases are probably not recognized and therefore not reported as tricyclic/cardiac deaths.

There are no up-to-date estimates of sufficient size to assess the present dangers of ECT. The frequently quoted figure of 1 in 28,000 individual treatments (Barker and Baker, 1959) is probably too high for patients as selected today; so no estimate of the dangers from ECT can be given.

About 15 per cent of individuals with affective disorder die by suicide (Guze and Robins, 1970), and a figure of six illnesses per lifetime has been assumed—a value which is probably an overestimate (Angst, 1976, personal communication). Thus the expectation of death by suicide may be in the region of 1 in 40 illnesses. The main criticism of using this figure in the present context (apart from the assumption of six illnesses per lifetime) is that some of the patients particularly at risk for suicide will not

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

present for treatment and it may be hoped that if they had done so the risk would have been reduced. As an approximation, a 1 per cent risk of suicide per illness has been assumed in those patients seeking specialist help, i.e. 10,000 deaths per million illnesses. Even if the mean number of prescriptions per illness is very high, a comparison of this figure with Girdwood's data gives some idea, albeit uncertainly, of the gap between the hazards of the illness itself and those of the therapy. This exercise suggests the following conclusions:

(i) the need to treat depression;

(ii) the particularly high degree of safety of tricyclics, provided they are not given to patients with cardiac abnormalities;

(iii) the considerable risk of suicide in moderate or severe illness as compared with the hazards of any of the current remedies (including MAOI);

(iv) following from (iii), the need to give alternative therapy to tricyclic antidepressants, if these have failed, in an adequate 'trial' of these compounds;

(v) although the risk from MAOIs is greater than that from tricyclics, it is so much smaller than that from the illness itself that it is not in the interest of patients to withhold MAOIs if there are indications for their use.

Management of Depressive Phases

Patients suffering from depressive forms of affective illness present in a multiplicity of ways —the various symptoms of the illness itself, attempted suicide, marital or occupational problems, somatic symptoms, undefined ill health, social withdrawal and others. The initial illness in particular, if nobody has considered the possibility of affective illness, may not be diagnosed in its early stages. Atypical forms are often missed, and in adolescents and young people, where the pattern is often atypical, the illness may not be recognized and go untreated for some time.

Once the likelihood of the illness being that of depressive illness has been recognized and the diagnosis established, the first task is to assess the danger of suicide and the severity of illness. Many patients communicate their intention of killing themselves to a relative, friend or general practitioner, and many will be quite truthful if questioned directly about suicidal thoughts and the progression to the intention of doing so. Some express anxiety that the impulse will become too strong, and fear of an impulsive act may be justified. Severe depression, lack of insight, guilt, profound hopelessness, with the retention or regaining of sufficient energy and drive to put a plan into action are a dangerous combination, and account for the fact that many depressives who kill themselves have not reached the depths of depression or are in the first stages of recovery. Dependants, strong families ties and deeply held religious convictions will deter the patient from suicide, but only up to a certain point, and sometimes loved ones may be included in delusions of catastrophe and be put at risk by the intention of 'taking them with me'. Being single, divorced or widowed, previous attempts, the male sex, recent bereavement, heavy drinking and limited social contacts are all factors increasing the likelihood of suicide. Denial of suicidal thoughts in any moderately or severely depressed patient must be regarded as being untrue, as must denial of intent in others. Unfortunately, there are no completely hard and fast rules for judging this risk, and underestimation of the problem is often unavoidable.

Severity of illness is based on a total view of the clinical state. Its assessment includes depth of depression, thoughts of suicide and likelihood of there being intent to carry it out, the presence and severity of such symptoms as anxiety, agitation, delusions, loss of insight, prominent feelings of hopelessness and worthlessness, loss of weight and the number and profundity of other symptoms.

Very ill and suicidal patients must be admitted to hospital. For those less ill, a number of factors need to be taken into consideration, such as the attitude of the spouse and others in the family, the likelihood of the patient taking the prescribed medication, the degree of fatigue and disturbance in the members of the family, the possibility of the individual losing his or her job, availability of help and support from relatives and friends, the age of children.

If the spouse can accept the illness and 'allow the patient to be ill' for a time, if the patient feels

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

that he or she does not need to 'put on a front', and if responsibilities can be shed temporarily, then this seems to be a helpful environment for recovery as an out-patient. An individual with affective illness struggling to appear normal and at the same time attempting to maintain a job or do all the housework is in a particularly stressful situation, which seems to militate against a rapid or even successful return to normality.

Home and work conditions may balance the argument for or against out-patient therapy in the less than severely ill. For others, the day hospital may be the most suitable compromise. The advantages of in-patient treatment, as opposed, to say, weekly visits to an out-patient clinic, include: the fact that spontaneous improvement is seen in some patients soon after admission the close supervision and flexibility of drug and other therapy, freedom from outside stresses for the patient, the lessening of the burden on the family, the reduction in the risk of suicide, and the early detection of deterioration. The disadvantages are the usual and obvious ones: the general undesirability of admission to hospital, of removing a mother from a family, of possibly putting a job at risk and the risk in prolonged illness of undue dependence on the shelter of the hospital environment.

Whatever choice of therapeutic situation is made, all patients should be screened for physical illness. This should include physical examination, urinalysis, ESR, blood counts, blood sugar, blood urea, chest X-ray, WR, and assessment of thyroid function; an ECG should be done if there are any indications whatsoever.

Most patients experience relief at having their problems recognized and the prospect of having something done about them. At the earliest possible stage a social worker should meet and help those families disturbed and puzzled by their recent traumatic experiences and possibly in practical difficulties produced by the ill member.

Sometimes in the early stages of management of an episode of depression there is uncertainty about the evaluation of apparent problems presented by the patients. The patient may complain of difficulties and fears or even catastrophes connected with their families, marriage, job or housing, or of legal entanglements, bankruptcy, etc, any of which may be either delusional or real. A close relative or a friend may or may not be helpful, because sometimes they can be carried along by a patient's anxieties and systematized delusional systems. Sometimes the problems of an illness reach such a pitch that there is an apparent firm resolve to resign from a post, sell a house, get a divorce, etc—resolutions which disappear as the illness fades.

The social worker can usually help to assess the magnitude of a problem if the spouse or other informant has been confused by the patient's delusions. If possible, the patient and family should be persuaded to postpone decisions, especially those which have long-term effects, until the patient has regained insight and judgement. The social worker can maintain the morale of the family during treatment, can disentangle practical problems and can encourage the relatives to regain perspective and balance. They can show how to develop a non-punitive, accepting attitude to the patient during the illness and can push for the rebuilding of confidence and robust attitudes on the part of everybody concerned when the illness has passed.

Antidepressant Treatment

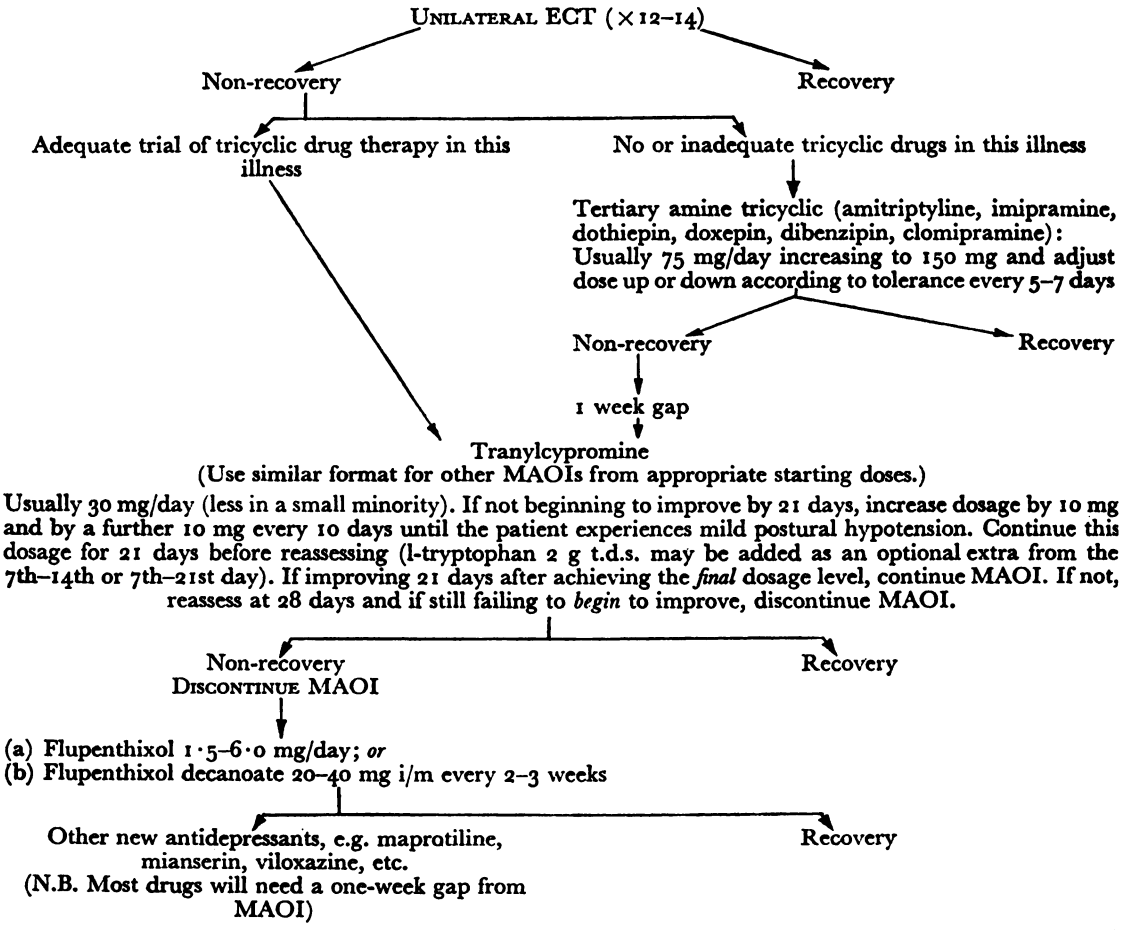
Schemes of treatment, based on currently available and established antidepressants and some of the newer compounds, are given in Tables II and III. The type of therapy chosen depends on severity of illness and the treatment given up to the time of referral. Many of the patients sent for specialist advice have been prescribed tricyclic antidepressants at varying doses, sometimes for very long periods, and the question always arises with these patients whether or not the treatment can be said to have failed.

Therapy with a tricyclic antidepressant can be said to have failed only if it has had an adequate trial. For the present this may be defined operationally as a period in which the drug has been taken consistently and in the case of a tertiary amine compound with a dosage which keeps the patient experiencing mild side effects for a minimum of four weeks. For a secondary amine tricyclic drug, an ade-

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

TABLE II

Suggested treatment schedule
Severe and some moderately depressed patients



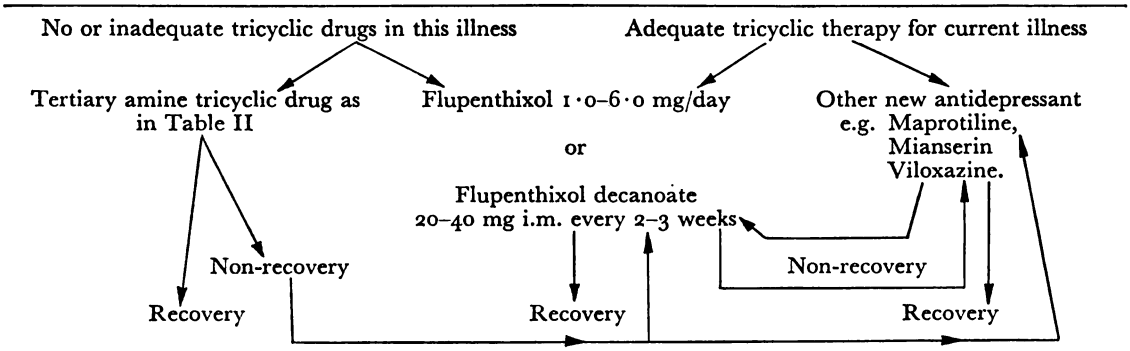
quate trial may at present be considered as four weeks of therapy, keeping the patient at a dosage giving mild side effects, and then a period of 7–10 days at a slightly lower dosage. Because of their efficiency and safety in patients without heart disease, tricyclic antidepressants are the initial treatment of choice for individuals who have not had an adequate trial of them, and who are mildly or sometimes moderately ill.

Most clinicians start with a low dose of a drug such as amitriptyline 75 mg. Giving the drug in a single dose at night has advantages (Pearce and Linford Rees, 1974). This can be increased to 150 mg/daily after 3–4 days. Some will require more than this and some less, according to their metabolic patterns, but the dose should be readjusted at least weekly and preferably more frequently to keep the patient experiencing mild side effects,* such as difficulty in accommodation and postural hypo-

* This does not imply a relationship between side effects and therapeutic action—the aim with tertiary amine tricyclic antidepressants is to reach the maximum tolerable dose, and side effects are the practical bar which determines this dosage.

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

TABLE III
Suggested treatment schedule
Mild and some moderately ill depressed patients



tension (dryness of the mouth is too early and universal a symptom to be of much use in this context). Patients should be told that they will experience and should expect side effects when the drug reaches an effective level and also that recovery takes several weeks.

If a patient is not beginning to improve after 28 days and has been taking the tricyclic drug continuously at a carefully adjusted level of dosage, it is unlikely to be effective in that individual, and there is little or no point in continuing with the drug. There is certainly no justification for continuing with more than five weeks' treatment with a tricyclic antidepressant at the very most if the illness is not beginning to remit by that time, unless the policy is to minister to the doctor's need to allay his own anxieties until a natural remission occurs. Some clinicians try to raise the dosage slightly, and this may be worth trying for a brief period. Others change from a tertiary to a secondary amine tricyclic for a further two weeks' trial, but there is little evidence to suggest that this is a particularly beneficial line of action.

In a patient presenting in out-patients on a high dose of nortriptyline, or possibly some other secondary amine tricyclic, who is failing to respond, the dosage can be reduced slightly for 7–10 days in case the plasma level is in the ineffective high region.

Electroconvulsive Therapy (ECT)

The most severely ill patients and some of those with moderately severe depression should be given ECT as the initial treatment of choice. For actively suicidal, severely deluded, very agitated or retarded patients, 3–4 unilateral ECTs may be given in the first week, followed by a lesser frequency of treatment (2–3/week) up to a total of 12–14 treatments. Less disturbed patients can be treated twice a week from the outset.

There are exceptions, but a favourable sign is transient improvement immediately after treatment, and failure of this to begin to appear after a few treatments is not a good prognostic sign for this mode of therapy.

Depending on the drugs they are receiving, the nature and severity of the lesions present, and a physician's or an anaesthetist's advice, ECT may be the best initial treatment for patients with cardiac disease or hypertension. If ECT is contraindicated, other therapies (e.g. isocarboxazid, fluanxol) may be appropriate, but again there should be consultation with the physician looking after the patient.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are still unacceptable to some clinicians because of their interactions with foods and drugs. However, the attempt here made at an assessment of relative hazards shows that although there is real need for care in the use of these drugs, it would be wrong to withhold them when and where they are indicated. Obviously, they are not suitable for some patients, such as those who are unable to follow the dietary/drug

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

precautions, and, like other drugs, they can be used for attempts at self-destruction.

Some care in their use is needed also with arteriosclerotic patients because of postural hypotension, and they should not be given to patients with liver disease. Many referred patients have received tricyclic antidepressants unsuccessfully, so that if this treatment has been adequate the psychiatrist is faced with the choice of ECT or trying one of the newer drugs or MAOI. The areas of therapeutic overlap of the new antidepressant therapies with the older remedies are unknown.

A relatively uncommon problem is that of patients who cannot tolerate tricyclic antidepressants, even in small doses, and whose experience of these drugs is so unpleasant that they are loath to try any similar compound again. Such individuals may accept treatment with MAOI in preference to other drugs, but the decision to give this class of compound may depend on severity and/or the urgency of bringing the time of recovery down to a minimum.

Most clinicians who use MAOIs give tranylcypromine, phenelzine, or isocarboxazid. Where there are no facilities for distinguishing fast from slow acetylators, and indeed whilst the problem of variable metabolism of phenelzine exists, the choice of MAOI therapy might be tranylcypromine, used in variable dosage according to needs. Alternatively, phenelzine can be given, but obviously dosage must be adjusted even more flexibly if therapeutic levels are to be achieved. Isocarboxazid, as a less active drug than tranylcypromine, is of particular use for the older patient in a dose range starting in the region of 20–30 mg/day.

Tranylcypromine can be taken as the model for mode of adjustment of dosage. Because of its stimulant action in most patients it is customary to divide it between morning and 12 mid-day doses, initially giving 20 mg in the morning and 10 mg at mid-day (or 10 mg b.d. in smaller individuals). Assessment of progress at 21 days should give some indication of whether the dose needs increasing. If the patient is improving, nothing more needs to be done. If he or she has not even begun to show improvement in mood, etc at 21 days *and* is experiencing side effects, the drug is unlikely to be of benefit. If, on the other hand, the patient is clinically static and has no trace of postural hypotension, the dose should be increased to 40 mg per day —20 mg in the morning and 20 mg at mid-day. The process of assessment can be repeated 10 days later, again increasing the dose by 10 mg if no side effects appear, and so on until some patients may be taking 60 mg per day or more. The aim is to bring the patient gradually to the point at which he is receiving sufficient MAOI to give mild postural hypotension. It is only at 21 days after this point that it is possible to assess whether or not the drug is likely to work in the case of that individual. If MAOI is going to help, the patient should be showing at least the early signs of improvement 21 days after reaching the 'side effect' dosage. Of course, many recover on 30 mg/day, but a scheme of the kind described here is necessary for those whose metabolic patterns necessitate more than the basic dosage level.

Therapy should be continued for several weeks after complete recovery and then 'tailed off' cautiously, and dietary precautions should be prolonged for one week after discontinuing treatment. Some patients need more prolonged treatment, and a minority make an initial 'recovery' but go on improving clinically for many weeks afterwards if the MAOI is continued.

Before starting therapy, the patient should be instructed in dietary and drug precautions, and he should carry a card giving instructions, etc, similar to the one shown in Appendix 1.

New Antidepressants

Flupenthixol

This is an interesting compound reported to have antidepressant qualities in a recent double blind trial in out-patients (Young, Hughes and Lader, 1976). It has very low toxicity, which may make it suitable for the elderly (Hall, 1974) as well as for younger patients, and it has the advantage that it is given by depot injection as flupenthixol decanoate.

Maprotiline

Maprotiline is one of a new family of tetracyclic compounds reported to have anti-

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

depressant qualities (Forrest, 1975; Kielholz, 1972); it is said to have mild side effects.

Mianserin

This is a tetracyclic with an unusual pharmacological profile for an antidepressant, and is claimed to have a low incidence of side effects (Kopera, 1975; Coppen, Gupta, Montgomery, Ghose, Bailey, Burns and DeRidder, 1976).

Viloxazine

This does not have the side effects usually expected of antidepressants. It can give rise to nausea and vomiting in some individuals, but is claimed to act quickly in those individuals who respond to it (Pichot, Guelfi and Dreyfus, 1975; Mahapatra, 1975).

Trazodone

This is a new compound reported to have both antidepressant and anxiolytic activity (Wheatley, 1976). It is likely to become available in the U.K. in 1977.

Nomifensine

Nomifensine is another new compound likely to be in use in the U.K. in 1977. It is reported to have antidepressant and anxiolytic properties (Forrest, Nicholson and Hewett, 1976).

Use of Hypnotics and Tranquillizers in Depression

As discussed above, it is advisable to avoid polypharmacy in the treatment of depression. Besides the reasons already given there is also one connected with an area not discussed here —the fact that we do not know whether major tranquillizers help or hinder pharmacologically in antidepressant treatment. Obviously, however, phenothiazines or butyrophenones have to be given to some very agitated or deluded patients. Disturbance of sleep is almost universal in depressive affective illness, and here sedative tricyclic drugs given at night may help. Otherwise, nitrazepam or chloral hydrate are the most useful, although they rarely solve the problem completely.

Manic Episodes

Depression is a most disruptive and painful illness for both the patient and the family, but from some points of view mania at its extremes can be more damaging and destructive. Most of the general points in management and in helping the family discussed for depression apply also to manic patients, though the type of strain put on the family and the problems created are likely to be different. Manic individuals may be difficult to contain, may cause anxiety about their physical stamina, and may be extremely wearing to all concerned, including other patients. Yet therapy of the episode is usually fairly straightforward. Mania and hypomania are very variable conditions from day to day, but if the patient has retained some insight and control he can usually be managed as an out-patient. Once control has worn thin, in-patient treatment becomes necessary.

In the treatment of mania, it should be appreciated that 'set' dosages of drugs do not apply. The needs of patients are dictated not only by variations in their metabolism of drugs but also by the severity of the mania, which in part determines the patient's tolerance of the drug therapy.

The first line of attack is the use of the major tranquillizers, which act relatively quickly and allow time for the more leisurely introduction of lithium. Since the initial control of illness is going to depend on tranquillizers, and the effects of lithium may take a week to appear, there is no point in taking heroic measures designed to give therapeutic levels of lithium 'overnight'. The main use of lithium is that it may allow withdrawal of the tranquillizers at an earlier time than otherwise would be possible.

Patients with the most severe mania need bringing under at least partial control as quickly as possible. Small, frail patients and the elderly should be given lower doses, but other patients with mania may need an initial dose of 10–30 mg haloperidol i/m, this being the initial drug of choice. Many clinicians now await symptoms of extrapyramidal side effects before prescribing antiparkinsonian drugs, and this is probably advisable.

After 1–1½ hours, a further dose of haloperidol can be given, the dose being judged on

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

response to the first injection. The main contraindication to continuing at high dosage is a fall in the systolic blood pressure to below 100 mm, but hypotension is not usually a major problem with haloperidol. Otherwise, the injections can be repeated at 1–1½ hour intervals until the mania subsides. A few may require 40–100 mg of haloperidol per day (or even more) to control the first few days of illness at its height, but in most the condition responds to the 40–60 mg/ daily range.

The patient should be switched to oral therapy as soon as possible, using the daily parenteral dose as a starting guide to dosage, the oral dose for haloperidol being about twice the amount given parenterally. Antiparkinsonian medication can also be given orally, if needed. At this stage lithium treatment should be begun. Here the aim is to be temporarily at the upper end of the therapeutic range of 0·8–1·2 mM/L or even slightly higher in young people. A dose of 1,000–1,200 mg can be given daily in divided doses, readjusting this if tremor or other side effects appear. Otherwise, the dose can be raised or lowered, according to the serum level (taken 12 hours after the previous dose) 5 days after beginning lithium treatment. After readjusting the dose, the serum level and dosage should be checked 5–6 days later.

Once the condition begins to subside, it is most important to reduce dosages in step, because tolerance to neuroleptics and lithium decreases, and delays and lack of flexibility in altering therapy can cause the patient unnecessary discomfort.

With return to near normal mood, neuroleptics should already have been reduced, and the amounts of lithium given should have been adjusted to give the usual therapeutic range. Neuroleptics should be withdrawn altogether a short while later and lithium can be continued either for a few weeks or indefinitely if the previous history suggests a need for long-term maintenance treatment.

A similar format to the one above can be used for chlorpromazine for the treatment of severe mania not responding to haloperidol, but rather more caution is needed. It is wise to give a test dose of chlorpromazine of 10 mg i/m at the outset (Man and Chen, 1973) and monitor blood pressure to find out if the patient is unusually sensitive to the hypotensive effect of this drug. If there is no such effect within 1–1½ hours, the patient can be given 50–75 mg chlorpromazine i/m every ½ to ¾ hour until the symptoms begin to subside, monitoring blood pressure throughout. Again, antiparkinsonian drugs should be given as needed, and the daily parenteral dose can be taken as an approximate (low) estimate of what should be given orally.

Hypomanic patients are easier to treat, in that therapy can be oral from the outset, with oral antiparkinsonian agents, if required, and many individuals can be managed as outpatients. The initial dose of haloperidol or chlorpromazine can be low and increased every 12 or 24 hours until there is a therapeutic effect. For instance, with haloperidol for most patients the daily dose may lie between 3–20 mg. Lithium should be incorporated in the treatment for most individuals. Some mildly hypomanic patients can be treated with lithium only.

Mania in the elderly should be treated with low doses of haloperidol intramuscularly in the range of 0·25–5 mg, with monitoring of blood pressure thereafter. According to response, a further dose can be given every 1½–2 hours, increasing the amount given if necessary sometimes up to the 20–30 mg/day level. Of course, many patients will show subsidence of symptoms at much lower dosage levels.

Daily reassessment of the amount given is needed, especially when the episode of mania is subsiding. Antiparkinsonian drugs can be added if necessary and oral therapy substituted at the earliest possible time.

Because of the difficulties in giving lithium to elderly disturbed patients with variable food and fluid intake and reduced renal function, it is usually preferable not to give lithium or to postpone the decision for a later assessment.

Resistant Depression

By resistant depression is meant an episode which once established does not respond to tricyclic antidepressants, ECT or MAOI. This is not an uncommon problem, since a few per cent of patients diagnosed as having depressive affective disorder ultimately come

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

into this category. It is not known how many patients in the population at large pass into perhaps a milder but still resistant depression which does not remit spontaneously, or into persistently recurrent illness not ameliorated by the techniques discussed.

For the more profound episodes of resistant illness, the problem is a most serious one. If the illness does not remit early, with or without medical help, and illness is prolonged from months to a year or longer, then ultimately physical and psychological deterioration must follow (if the patient does not die by suicide in the meantime).

It is helpful to start afresh, as though the patient were a newly presenting case. The history is re-examined, and if new relevant points appear they should be explored. The original diagnosis should be reassessed and a new look taken at home and work problems, etc. The patient should be re-examined physically, including the laboratory and other tests, in an attempt to exclude physical illness, especially endocrine, neoplastic or deficiency diseases. A small but significant proportion of cases do prove to have extraneous factors. Of the remainder, some emerge from their illness at some stage of a careful and thorough programme of repeated treatments as suggested and set out in the flow diagram in Table IV. Each phase of treatment must be carried through with the greatest care to ensure that dosages are tailored to individual needs.

For the ultimate therapeutic failures, the choice is between long or even permanent illness and stereotactic tractotomy. This offers the carefully diagnosed and selected patients a reasonable prospect of relieving their symptoms, particularly those with unipolar illness. The situation with bipolar illness seems less clarified to date.

TABLE IV

Suggested treatment schedule
Resistant depression

Reassess history, psychosocial factors, physical state. Irrespective of earlier therapy, carry out the following treatments:

(a) Night sedation with benzodiazepines only and give no other drugs for 2–4 weeks.
Unilateral or bilateral ECT × 12–14.

↓

(b) Tertiary amine tricyclic drug pushed to limit of tolerance. Readjust dosage every 4–5 days. Check drug being taken regularly. Assess at 28 and 35 days. Stop if not improving by 35th day.

↓ (1 week gap after stopping tricyclic drug)

(c) Tranylcypromine 30 mg. Increase dose by 10 mg every 10 days until experiencing definite postural hypotension. After 1 week at this dose add l-tryptophan 2 g t.d.s. Assess at 28 days. If not beginning to improve by this date, discontinue both drugs.

↓ (*MAOI stopped*)

(d) Flupenthixol 1·5 increasing to 4·5–6 mg/day for a minimum of 3 weeks.

↓

(e) Combined antidepressants, e.g.:
Amitriptyline 75–150 mg at night;
Tranylcypromine 20 mg in the morning
10 mg at mid-day.
Assess at 28 and 35 days and stop if not beginning to improve.

↓

1 week free from drugs if others drugs to be given

→ or

Await natural remission

Stereotactic tractotomy for unipolar patients (? bipolar as well)

Treatment in Recurrent Illness

Angst and his co-workers have shown that successive cycles in affective disorder tend to get shorter, i.e. frequency of illness increases with time (Grof, Schou, Angst, Baastrup and Weis, 1970). Of course, many individuals, especially those with unipolar illness, have very few episodes in their lives, and indeed it is likely that many individuals with susceptibility do not manifest the disorder at all. In others, whose susceptibility to illness is presumably combined with a low threshold to episodic attacks, illnesses tend to occur with progressively shorter intervals between them. Bipolar affective disorder, because of its rela-

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

tively early onset and short cycle length (Grof *et al*, 1970) is perhaps the more malign illness of the two forms.

The problem with an illness which tends to have a statistically worsening pattern with age, but in which inter- and intra-individual patterns show such wide variations, is to decide at what point measures should be undertaken to try to prevent recurrence. Some patients, having heard of lithium, may request it after one particularly serious, dangerous or semi-resistant episode. Most centres, however, will bring the possibility of therapy with lithium or tricyclics to the patient's notice only after there have been two or possibly three discrete episodes of illness in two years.

Trials of lithium as maintenance therapy in affective disorders have included those by Baastrup and Schou, 1967; Angst, Weis, Grof, Baastrup and Schou, 1970; Melia, 1970; Coppen, Noguera, Bailey, Burns, Swani, Hare and Gardner, 1971; and Hullin, McDonald and Allsopp, 1972. The data from these and other studies suggest that lithium is effective in both unipolar and bipolar illness (Davis, 1976).

Tricyclic antidepressant drugs also are of use as maintenance therapy in depressive illness (Seager and Bird, 1962; and Kay, Fahy and Garside, 1970). Mindham, Howland and Shepherd (1973) have shown that giving tricyclic antidepressants (imipramine or amitriptyline) for the six months following an episode of depression reduces the risk of early relapse to a significant degree. Other workers have demonstrated the use of amitriptyline in preventing relapses in out-patients presenting with depression (Klerman, DiMascio, Weissman, Prusoff and Paykel, 1974; and Paykel, DiMascio, Haskell and Prusoff, 1975). According to the findings of Prien, Klett and Caffey (1973), tricyclic antidepressants were not suitable for maintenance treatment of bipolar patients because they did not prevent relapse into mania. On the other hand, in their study the tricyclic used, imipramine, did protect unipolar patients from relapse.

Sometimes tricyclic drugs may be given for several months to prevent relapse into depressive illness in what is thought to be a susceptible period of a patient's life, i.e. just after an episode. Such patients may not merit or may not agree to long-term treatment.

Long-term therapy with lithium salts (bipolar and unipolar patients) or tricyclic antidepressants (unipolar patients) may be considered initially at different stages of the illness by different clinicians. The decision to start must be a joint one by both patient and doctor after an explanation of the advantages and disadvantages of therapy versus non-therapy. The application needed during therapy by the patient is considerable and will require long term motivation and conscientiousness on his part.

If after discussion the patient wishes to undertake treatment with lithium, the first step is to look for renal or cardiac disease and to make sure that the patient is not in the first three months of pregnancy or planning a pregnancy. It is wise to assess thyroid function. If the patient has no renal or significant cardiovascular disease, the procedure for initiating and maintaining therapy then is as shown in Table V (based on a similar table in Schou and Shaw, 1973).

The patient should have an instruction sheet along the lines shown in Appendix 3 (based on a similar sheet written by Schou, Amdisen and Baastrup, 1971). The patient should be warned of side and toxic effects (Table VI) and should have extra blood tests, if they appear, 6–7 days after a change in dose, during and after other illnesses, if other conditions result in change in sodium intake, if diuretics must be taken and during and after parturition. Thyroid function should be assessed yearly. Lithium should be stopped immediately if a woman becomes pregnant and should also be discontinued if acute renal disease develops.

Tremor can be managed by decreasing the dose slightly, if this still leaves the patient within the therapeutic range of 0·8–1·2 mM/L*. Propranolol will abolish the tremor, or may be reserved for special occasions by patients who otherwise will tolerate a degree of tremor. Sometimes looseness of the stools persists and may lead to patients discontinuing therapy.

* All serum lithium levels must be exactly 12 hrs after the last dose.

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

TABLE V

Procedure for maintenance treatment with lithium

Time	Action	Comment
Pretreatment	Perform ordinary medical examination. Do blood urea and thyroid function tests. Send urine for analysis. Instruct the patient	Relative contraindications: renal disease, cardiac disease, planned pregnancy
Day 0	Start treatment with low daily dosage, e.g. 10 or 15 millimoles	'Ordinary' preparation: two or three doses during the day, morning (afternoon), bedtime. Sustained-release preparation: two daily doses, morning, bedtime
Day 7	Serum for lithium determination: blood sample drawn *12 hours after last intake of lithium*	Adjust dosage to give 0·7–1·2 mM/L. This is on simple *pro rata* basis: e.g. if serum level is 0·3 mM/L, tripling the dose will bring the level to around 0·9 mM/L
Days 14, 21 and 28	Serum for lithium determination: blood sample drawn *12 hours after last intake of lithium*	Adjust dosage as above
Hereafter at intervals, e.g. every 6 weeks (or longer in reliable, well-instructed patients)	Serum lithium control as above	If necessary, readjust dosage individually to find the serum-lithium level which for that patient gives full prophylactic protection with a minimum of side-effects. Maintain this serum-lithium level by means of regular blood checks
Yearly	Assess thyroid function	

[Based on Schou and Shaw, 1973; see also Amdisen, 1975]

TABLE VI

Different types of side-effect which may occur during lithium treatment

Side-effect	Initial, harmless	Persistent, harmless	Prodromes of intoxication
Nausea, loose stools	+	+	−
Vomiting, diarrhoea	−	−	+
Fine tremor of the hands	+	+	−
Coarse tremor of the hands	−	−	+
Polyuria and polydipsia	+	+	−
Weight gain	−	+	−
Oedema	−	+	−
Sluggishness, sleepiness	−	−	+
Vertigo	−	−	+
Dysarthria	−	−	+

[Reprinted from Schou and Shaw, 1973]

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

A small proportion of patients develop goitre during lithium therapy. This can be dealt with satisfactorily with small doses of thyroxine 0·1–0·2 mg daily, or alternatively lithium must be discontinued.

There is evidence that benefit from lithium therapy is cumulative with time (Schou *et al*, 1971) and may not develop fully for the first 6 or 12 months, so it is important that therapy should be continued on through any early relapses. In addition, some patients with very frequent recurrences who do not benefit by the abolition of attacks may experience less severe or less frequent illnesses. For unipolar patients, as mentioned above, tricyclic drugs are worth considering on a long-term basis for patients who prefer these drugs, or who have side effects from or who fail to benefit by lithium. The daily dose of the tricyclic drug should be that which produces minimal side effects or just below this dosage level.

Duration of therapy is a matter frequently raised by both patients and clinicians. If the patient is at risk for frequent attacks of affective illness, the duration of therapy with lithium should be unlimited. If, however, the original decision to start treatment was on doubtful grounds, then both the patient and doctor may lack the motivation to continue treatment after a while. It is important, therefore, to be clear on the indications for starting therapy.

Conclusions

It would be foolish to pretend that the means at our disposal for the treatment of affective illness are ideal. We may hope that the next decade will witness the introduction of more effective, rapid and comfortable remedies. Such hopes, however, do not relieve us of the obligation to exploit to the full the capabilities of the therapies we have now. They may not act speedily, and some have unpleasant side effects, but when tailored flexibly to the patient's needs, when given sequentially without undue prolongation of any single treatment which clearly is going to be ineffective, they relieve the majority of patients with these episodes.

Given a fair degree of confidence in the possibility of success with the 'anti-episode' and maintenance therapies, the team can turn to other means of helping patients and supporting their families, and can seek to undo some of the disruption which has been produced by the illness.

Acknowledgements

I should like to thank Professor K. Rawnsley, Professor M. Schou, Dr P. Bridges, Dr M. Massey Stewart, Dr J. L. Lunn and Dr G. Pryce for their useful criticisms, and Mrs D. Barrett for her secretarial assistance. The author is a member of the external scientific staff of the Medical Research Council and is supported on an MRC Programme Grant.

References

ANGST, J., WEISS, P., GROF, P., BAASTRUP, P. C. & SCHOU, M. (1970) Lithium prophylaxis in recurrent affective disorders. *British Journal of Psychiatry*, **116**, 606–14.

AMDISEN, A. (1975). Monitoring of lithium treatment through determination of lithium concentration. *Danish Medical Bulletin*, **22**, 277–291.

ÅSBERG, M., CRÖNHOLM, B., SJÖQVIST, F. & TUCK, D. (1970) Correlation of subjective side effects with plasma concentrations of nortriptyline. *British Medical Journal*, *iv*, 18–21.

—— —— —— —— (1971) Relationship between plasma level and therapeutic effect of nortriptyline. *British Medical Journal*, *iii*, 331–4.

BAASTRUP, P. C. & SCHOU, M. (1967) Lithium as a prophylactic agent. Its effect against recurrent depression and manic-depressive psychosis. *Archives of General Psychiatry*, **16**, 162–72.

BARKER, J. C. & BAKER, A. A. (1959) Deaths associated with electroplexy. *Journal of Mental Science*, **105**, 339–48.

BELLWARD, G. D. & MORGAN, R. G. (1972) Drug interaction with liver microsomal drug metabolizing enzymes: Imipramine and norethindrone. *Canadian Federation of Biological Societies*, **15**, Abstract 63.

BOAKES, A. J. (1971) Monoamine oxidase inhibitors—interactions with other drugs and foodstuffs. *Prescribers' Journal*, **11**, 109–15.

—— (1974) The interaction of MAOI and tricyclic antidepressants with foodstuffs and other drugs. *Colloquium on MAOI therapy*. Warner Brothers Publication, 82–107.

BRAITHWAITE, R. A., GOULDING, R., THEANO, G., BAILEY, J. & COPPEN, A. (1972) Plasma concentration of amitriptyline and clinical response. *Lancet*, *i*, 1297–1300.

BROADHURST, A. D. (1970) L-tryptophan verus ECT. *Lancet*, *i*, 1392–3.

CARROLL, B. J., MOWBRAY, R. M. & DAVIES, B. (1970) Sequential comparison of l-tryptophan with ECT in severe depression. *Lancet*, *i*, 967–9.

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

COPPEN, A., GUPTA, R., MONTGOMERY, S., GHOSE, K., BAILEY, J., BURNS, B. & DERIDDER, J. J. (1976) Mianserin hydrochloride: a novel antidepressant. *British Journal of Psychiatry*, **129**, 342–5.

—— NOGUERA, R., BAILEY, J., BURNS, B., SWANI, M., HARE, E. & GARDNER, R. (1971) Prophylactic lithium in affective disorders—a controlled trial. *Lancet*, *ii*, 275–9.

—— PRANGE, A. J., WHYBROW, P. C., NOGUERA, R. & MAGGS, R. (1972) The comparative antidepressant effect of l-tryptophan with and without attempted potentiation by liothyronine. *Archives of General Psychiatry*, **26**, 234–41.

—— SHAW, D. M. & FARRELL, J. P. (1963) Potentiation of the antidepressant effect of a monoamine-oxidase inhibitor by tryptophan. *Lancet*, *i*, 79–81.

—— —— HERZBERG, B. & MAGGS, R. (1967) Tryptophan in the treatment of depression. *Lancet*, *ii*, 1178–80.

CRAMMER, J. L., SCOTT, B. & ROLFE, B. (1969) Metabolism of ^{14}C-imipramine: II. Urinary metabolites in man. *Psychopharmacologia*, **15**, 207–25.

CUCINELL, S. A., CONNEY, A. H., SANSUR, M. & BURNS, J. J. (1965) Drug interactions in man: I. Lowering effect of phenobarbital on plasma levels of Bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clinical Pharmacology and Therapeutics*, **6**, 420–9.

DAVIDSON, S. J. (1976) Psychotropic drugs, stress and cardiomyopathies. Communication to *British Association for Psychopharmacology*, April 1976.
See also:

DAVIDSON, S. J. (& PROF. INNES) (1976) Psychotropic drugs, stress and cardiomyopathies. In *Stress and the Heart* (ed. D. Wheatley). New York: Raven Press, 1977.

DAVIS, J. M. (1976) Overview: Maintenance therapy in psychiatry. II. Affective disorders. *American Journal of Psychiatry*, **133**, 1–13.

DAYTON, P. G. & PEREL, J. M. (1971) Physiological and physiochemical bases of drug interactions in man. *Annals of the New York Academy of Sciences*, **179**, 67–87.

DUNNER, D. L. & GOODWIN, F. K. (1972) Effect of l-tryptophan on brain serotonin metabolism in depressed patients. *Archives of General Psychiatry*, **26**, 364–6.

FLEMENBAUM, A. (1971) Methylphenidate: a catalyst for the tricyclic antidepressants? *American Journal of Psychiatry*, **128**, 239.

FORREST, A., NICHOLSON, P. & HEWETT, A. (1976) A controlled randomized group comparison of the new isoquinoline nomifensine and imipramine in depressive illness. In press.

—— (1975) Maprotiline (Ludiomil) in depression: a report on a hospital monitored release study. In *Research and Clinical Investigation in Depression* (ed. J. E. Murphy). Northampton: Cambridge Medical Publications Ltd.

GIRDWOOD, R. H. (1974) Death after taking medicaments. *British Medical Journal*, *i*, 501–4.

GLASSMAN, A. H. & PLATMAN, S. R. (1969) Potentiation of a monoamine oxidase inhibitor by tryptophan. *Journal of Psychiatric Research*, **7**, 83–8.

—— (1973) The clinical pharmacology of imipramine. *Archives of General Psychiatry*, **28**, 649–53.

GRAM, L. F. & OVERØ, K. F. (1972) Drug interaction: inhibitory effect of neuroleptics on metabolism of tricyclic antidepressants in man. *British Medical Journal*, *i*, 463–5.

GRAM, L. F. REISBY, N., IBSEN, I., NAGY, A., DENCKER, S. J., BECK, P., PETERSEN, G. O. & CHRISTIANSEN, J. (1976) Plasma levels and antidepressant effect of imipramine. *Clinical Pharmacology and Therapeutics*, **19**, 318–24.

GROF, P., SCHOU, N., ANGST, J., BAASTRUP, P. C. & WEIS, P. (1970) Methodological problems of prophylactic trials in recurrent affective disorders. *British Journal of Psychiatry*, **116**, 599–603.

GUTIÉRREZ, J. L. A. & LÓPEZ IBOR ALIÑO, J. J. (1971) Tryptophan and a MAOI (Nialamide) in the treatment of depression. *International Pharmacopsychiatry*, **6**, 92–7.

GUZE, S. B. & ROBINS, E. (1970) Suicide and primary affective disorders. *British Journal of Psychiatry*, **117**, 437–8.

HALL, P. (1974) Differential diagnosis and treatment of depression in the elderly. *Gerontologia Clinica*, **16**, 126–36.

HERRINGTON, R. N., BRUCE, A., JOHNSTONE, E. C. & LADER, M. H. (1974) A comparative trial of l-tryptophan and ECT in severe depressive illness. *Lancet*, *ii*, 731–4.

—— —— —— —— (1976) Comparative trial of L-tryptophan and amitriptyline in depressive illness. *Psychological Medicine*, **6**, 673–78.

HULLIN, R. P., MCDONALD, R. & ALLSOP, M. N. E. (1972) Prophylactic lithium in recurrent affective disorders. *Lancet*, *i*, 1044–6.

JOHNSTONE, E. C. (1974) The relationship between response to phenalzine and acetylator status in depressed patients. In *Colloquium on MAOI Therapy*, pp 40–53. William Warner Publication.

KATO, R., CHIESARA, E. & VASSANELLI, P. (1963) Mechanism of potentiation of barbiturates and meprobamate actions by imipramine. *Biochemical Pharmacology*, **12**, 357–64.

KAY, D. W. K., FAHY, T. & GARSIDE, R. F. (1970) A seven month double-blind trial of amitriptyline and diazepam in ECT treated depressed patients. *British Journal of Psychiatry*, **117**, 667–71.

KIELHOLZ, P. (Ed.) (1972) *Depressive Illness: Diagnosis, Assessment, Treatment*. Berne: Hans Huber Publishing.

KLERMAN, G. L., DIMASCIO, A., WEISSMAN, M., PRUSOFF, B. A. & PAYKEL, E. S. (1974) Treatment of depression by drugs and psychotherapy. *American Journal of Psychiatry*, **131**, 186–91.

KOPERA, H. (1975) Aspects of clinical pharmacology and clinical experiences with Org GB 94. In *Depressive Illness and Experiences with a New Antidepressant Drug GB94* (ed. T. Vossenaar), pp 26–43. Amsterdam: Excerpta Medica.

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

KRAGH-SØRENSEN, P., ÅSBERG, M. & EGGERT-HANSEN, C. (1973) Plasma-nortriptyline levels in endogenous depression. *Lancet*, *i*, 113–15.

LADER, M. H. (1976) Clinical psychopharmacology. In *Recent Advances in Clinical Psychiatry No. 2* (ed. K. Granville-Grossman), pp 1–30. Edinburgh: Churchill Livingstone.

LANCET (1965) Leading article: Combining the antidepressant drugs. *Lancet*, *ii*, 118.

LIPSEDGE, M. (1976) Drug treatment. In *Recent Advances in Clinical Psychiatry No. 2* (ed. K. Granville-Grossman), pp 31–51. Edinburgh: Churchill Livingstone.

MACDONALD, M. G. & ROBINSON, D. S. (1968) Clinical observations of possible barbiturate interference with anticoagulation. *Journal of the American Medical Association*, **204**, 97–100.

MAHAPATRA, S. B. (1975) Short term effects of viloxazine (Vivalan) compared with placebo in depression: a double-blind study. *Journal of the International Medical Research*, **3**, Suppl. (3), 70–4.

MAN, P. L. & CHEN, D. H. (1973) Rapid tranquillization of acutely psychotic patients with intramuscular haloperidol and chlorpromazine. *Psychosomatics*, **14**, 59–63.

MARSHALL, E. F. (1976) The myth of phenelzine acetylation. *British Medical Journal*, *ii*, 817.

MASSEY-STEWART, M. (1976) MAOIs and food—fact and fiction. *Adverse Drug Reaction Bulletin*, no. **58**, 200–3 (ed. D. M. Davis). Consett, Co. Durham: Adverse Drug Reaction Research Unit.

MELIA, P. I. (1970) Prophylactic lithium: a double-blind trial in recurrent affective disorders. *British Journal of Psychiatry*, **116**, 621–4.

MINDHAM, R. H. S., HOWLAND, C. & SHEPHERD, M. (1973) An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. *Psychological Medicine*, **3**, 5–17.

O'MALLEY, K., BROWNING, M., STEVENSON, I. & TURNBULL, M. J. (1973) Stimulation of drug metabolism in man by tricyclic antidepressants. *European Journal of Clinical Pharmacology*, **6**, 102–6.

PARE, C. M. B. (1963) Potentiation of monoamine-oxidase inhibitors by tryptophan. *Lancet*, *ii*, 527–8.

PAYKEL, E. S., DIMASCIO, A., HASKELL, D. & PRUSOFF, B. A. (1975) Effects of maintenance amitriptyline and psychotherapy on symptoms of depression. *Psychological Medicine*, **5**, 67–77.

PEARCE, J. B. & LINFORD REES, W. (1974) A double-blind comparison of three times daily and single night dosage of the tricyclic anti-depressant, dothiepin. *The Journal of International Medical Research*, **2**, 12–19.

PEDERSEN, V. & MØLLER NIELSEN, I. (1975) Hyperthermia in rabbits caused by interaction between MAOIs, antiparkinsonian drugs and neuroleptics. *Lancet*, *ii*, 409–11.

PICHOT, P., GUELFI, J. & DREFUS, J. F. (1975) A controlled multicentre therapeutic trial of viloxazine (Vivalan). *Journal of International Medical Research*, **3**, Suppl. (3), 80–6.

PRICE, J. (1967) Human polymorphism. *Journal of Medical Genetics*, **4**, 44–67.

PRIEN, R. F., KLETT, C. J. & CAFFEY, E. M. (1973) Lithium carbonate and imipramine in prevention of affective disorders. *Archives of General Psychiatry*, **29**, 420–5.

RAWLINS, M. D. (1974) Variability in response to drugs. *British Medical Journal*, *iv*, 91–4.

SCHOU, M., AMDISEN, A. & BAASTRUP, P. C. (1971) The practical management of lithium treatment. *British Journal of Hospital Medicine*, **6**, 53–60.

—— & SHAW, D. M. (1973) Lithium in recurrent manic-depressive disorders. *The Practitioner*, **210**, 105–11.

SCHUCKIT, M., ROBINS, E. & FEIGHNER, J. (1971) Tricyclic antidepressants and monoamine oxidase inhibitors. Combination therapy in the treatment of depression. *Archives of General Psychiatry*, **24**, 509–14.

SEAGER, C. P. & BIRD, R. L. (1962) Imipramine with electrical treatment in depression-controlled trial. *Journal of Mental Science*, **108**, 704–7.

SETHNA, E. R. (1974) A study of refractory cases of depressive illness and their response to combined antidepressant treatment. *British Journal of Psychiatry*, **124**, 265–72.

SHAND, D. G. & OATES, J. A. (1971) Metabolism of propanalol by rat liver microsomes and its inhibition by phenothiazine and tricyclic antidepressant drugs. *Biochemical Pharmacology*, **20**, 1720–3.

STOCKLEY, I. (1974) *Drug Interactions and their Mechanisms*. London: The Pharmaceutical Press.

WHARTON, R. N., PEREL, J. M., DAYTON, P. G. & MALITZ, S. (1971) A potential clinical use for methylphenidate with tricyclic antidepressants. *American Journal of Psychiatry*, **127**, 1619–25.

WHEATLEY, D. (1976) Evaluation of trazodone in the treatment of anxiety. *Current Therapeutic Research*, **20**, 74–83.

WHYTE, S. F., MACDONALD, A. J., NAYLOR, G. J. & MOODY, J. P. (1976) Plasma concentrations of protriptyline and clinical effects in depressed women. *British Journal of Psychiatry*, **128**, 384–90.

YOUNG, J. P. R., HUGHES, W. C. & LADER, M. H. (1976) A controlled comparison of flupenthixol and amitriptyline in depressed outpatients. *British Medical Journal*, *i*, 1116–18.

Appendix 1

INSTRUCTIONS TO PATIENTS

Please read this card carefully and carry it with you

PATIENT ON MAOI (Monoamine oxidase inhibitor)

FOOD

You must avoid:

Matured cheese in any form

Marmite, *Bovril* and similar yeast or meat extracts (beware drinks and stews made with these products)

Pickled herring

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

Alcohol in more than social, i.e. moderate, amounts (*limit yourself to two glasses of beer, wine or sherry. You may take more if you are drinking* only *spirits*).

Broad bean pods *and banana* skins

Food which is not fresh [*or freshly prepared from frozen or newly opened tinned food*]. Take special care to avoid non-fresh meat, fish, poultry, game or offal.

Any food which has given unpleasant symptoms previously.

MEDICINES

Do not take any *medicines, drugs, proprietary preparations* (*including cough and cold cures*) or any other medicament of any sort whatsoever without consulting your doctor.

Following these instructions (and carry this card with you) all the time whilst taking MAOI and continue to do so for a week after stopping MAOI.

Appendix 2

'FIRST AID' FOR TOXIC REACTIONS TO MAOI

INTRODUCTION

The most likely toxic reaction to MAOI is the 'cheese reaction' which is due to the presence of tyramine in this food. This is an indirect sympathomimetic agent which releases noradrenaline and adrenaline. The 'reaction' is due to the release of excessive amounts of catecholamines. Interacting drugs can give toxic reactions.

The most common reaction from tyramine is:
hypertension; headache;

More severe, but less common reactions may proceed to:
hypertension; headache;
muscle spasms;
hyperpyrexia (probably due to effect of amines on temperature control centres and contributed to by muscle spasms)

Complications include:
cerebral haemorrhage;
shock;
progressive hyperpyrexia.

If the less common but severe reactions are allowed to progress to complications, the patient may die. Speed is essential and the aim of first aid should be to treat the predominating toxic effect (usually hypertension)—or all if all three are present—and to transfer the patient to an intensive care unit as quickly as possible while the condition remains controllable.

TREATMENT: NEVER GIVE SYMPATHOMIMETIC AGENTS

(1) *Hypertension:* Treat when BP has risen to 180/100. Give phentolamine 5 mg i/v at intervals to keep BP below 180/100.
If the toxic reaction progresses beyond hypertension, treat as follows:

(2) *Hyperpyrexia:* Treat when temperature reaches 40 °C. Expose to fan, give tepid sponging, etc. If severe, cool limbs with ice.
I/m chlorpromazine—(probably resets temperature control mechanism and causes vasodilation of skin).

(3) *Muscle Spasms:* Treating this symptom could be difficult and ideally needs the assistance of an anaesthetist. As a first aid measure, therefore, give the treatment below only if you cannot control the temperature long enough to transfer the patient.
Give suxamethonium and ventilate the lungs with air or oxygen, using a bag and mask.
HAVE READY: Plasma and Cortisol in case shock supervenes.
NEVER GIVE SYMPATHOMIMETIC AMINES

Appendix 3

SUGGESTED ADVICE SHEET FOR PATIENTS ON LITHIUM

Lithium is a natural element used in the treatment of recurrent depressive or manic depressive illnesses. Some people with this illness may have one or more episodes but in others there are more frequent attacks.

Manic depressive illness (*bipolar affective disorder*)—*excited phase* (*hypomania or mania*)

This may be treated by lithium, other drugs or electrical treatment.

Depressed phase (*recurrent depressive or manic depressive illness*)

The episode itself is treated with drugs other than lithium.

Prevention of recurrence

Lithium may be used as a long-term treatment to prevent attacks of depression or mania if illnesses recur frequently.

The nature of the treatment

Lithium does not *cure* recurrent depressive or manic depressive illness, but it can *prevent recurrences* whilst the drug is taken or *make the attacks less severe or less frequent.* A successfully treated person simply feels well. You should therefore understand that this well-being depends on your continuing to take lithium as a sustained treatment. Any device which helps you to remember to take the tablets at the right time is of help. Forgotten tablets cannot be compensated for by a double dose next time. Lithium is not habit-forming.

Blood tests are necessary from time to time to maintain the correct amount of lithium in the body. The doctor judges the dosage that he will recommend to you on the basis of these blood tests.

Side effects

Lithium is a potent medicine and therefore may cause some side effects. These are usually temporary and mild, but should always be reported to the doctor at consultation. If, however, whilst you are on lithium you develop severe vomiting or diarrhoea, abnormal tiredness and dizziness,

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press

pronounced trembling of the hands or difficulty in speaking, you should inform your doctor immediately.

Other points

(1) Adjustment of dosage may be needed urgently if you have an illness like influenza, or lose appetite, or if you have to take diuretic drugs.

(2) You should not take special diets without consulting your doctor.

(3) If you plan a pregnancy or become pregnant, discontinue lithium.

(4) Benefit from lithium may take 6–12 months to appear, so you should take it continuously, even if there are episodes of illness in the early stages of treatment.

[Based on a similar sheet by Schou, Amdirsen and Baastrup, 1971.]

David M. Shaw, *Member of the External Scientific Staff of MRC; Department of Psychological Medicine, The Welsh National School of Medicine, Whitchurch Hospital, Cardiff CF4 7XB*

(*Received 9 November 1976*)

https://doi.org/10.1192/bjp.130.5.432 Published online by Cambridge University Press