MEDICAL PRACTICE

Today's Treatment

Psychological Medicine

Management of Depression

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British Medical Journal, 1975, 2, 372-376

Difficult Challenge

The treatment of severe depressive illness with drugs or electric convulsion therapy is relatively straightforward and because of the dramatic response to treatment provides satisfaction for the doctor and often appreciation from the patient. However, there are many types of depressive reactions which provide a difficult challenge to diagnostic and therapeutic skills and require subtle judgements on the relative importance of the environment, the patient's personality, and organic factors. Paradoxically these problems often involve patients in whom the symptoms are of a less acute nature though at times persistent or recurrent. Psychiatrists tend to have under their care a non-representative group of all depressed individuals, with disproportionate numbers of severely depressed patients or those with severe personality disorders. In this brief review of management an attempt will be made to give due attention to the commoner mild depressive groups, which will inevitably mean that less detailed examination of the severe depressive syndromes will be possible. The justification for this approach is that the latter are dealt with adequately in most standard texts on the subject.

Bereavement and Distress

It is obvious that depression is a normal human experience, yet

we must not underestimate the suffering from so-called normal depression, a particular example being the response to bereavement. As doctors we are called on to help relieve this suffering. A small part of such relief may be provided by the use of drugs, which are, however, required in only a small proportion of cases. In the early period of the grief some day-time sedation may be provided with a benzodiazepine. For example, diazepam (Valium) 5-10 mg three times daily is useful and sleep may be ensured by using nitrazepam (Mogadon) 10 mg at night. The risk of habituation to the benzodiazepines will be avoided if the period of administration is kept as short as possible. Prescription of night sedation should also be limited to the acute period of distress to minimize the risk of establishing the "hypnotic habit." When the immediate period of bereavement is over it is usual to withdraw drugs and to wait for the natural process of recovery. The normal grief reaction proceeds through two stages. First there is a withdrawal from forward-looking activities and a concentration on and preoccupation with past events, experience being dominated by memories of the dead person. After a time a period of exploration begins with a progressive reinvolverment in the process of living. While in most cases these adjustments proceed without specialist help, it should be acknowledged that the adequacy of the readjustment is variable, and many people may never again approach their pre-bereavement level.

Different societies approach the problem of bereavement in different ways. In some the outward expression of grief is encouraged, in others, such as ours, it is suppressed. In many families attempts to talk about the dead person are met with an embarrassed silence from the relatives. The doctor and minister are often expected to provide a professional service as listeners, and yet the skill of the listener is perhaps less important than his willingness to listen in a sympathetic fashion. It is important, therefore, to encourage the relatives and friends to play an active part in management. Feelings of anger and resentment may be

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directed against those who are trying to be of help, and these must be met with tolerance.

The role of antidepressant drugs in the management of grief reactions is far from clear. On rational grounds it seems unlikely that such treatment will be effective when the response is seen to be appropriate to the precipitating circumstance. Any effect seems likely to result from the sedative effect of the drugs rather than to a specific action on mood.

Complicated Bereavement Reactions

In some individuals the grief reaction does not undergo spontaneous resolution but instead progresses to a state where the clinical picture is identical with that of a depressive illness. How do we recognize when this has occurred? There can be no standard formula for making this decision. When the severity or duration of the reaction is excessive for that individual in that situation we need to consider the possibility that transition to a state of illness has occurred. The steps taken are the same as those in any clinical decision: an accurate analysis of the clinical state, an evaluation of the precipitating situation, such as closeness to the dead person, and a knowledge of the patient's previous personality. A prediction of the likely response can be made after assessing the appropriateness or abnormality of the patient's condition. In arriving at such a decision the doctor needs to bear in mind the range of mood response natural in the patient's society, and each case calls for the exercise of clinical judgement.

The response of some extended grief reactions to antidepressants may be dramatic, and even in doubtful cases it is justifiable to embark on a trial of treatment with the drugs.

Minor Depressive Episodes

If we take the grief reaction as a particular example of depression as a direct reaction to environmental precipitants, we can go on to consider other situations resulting in depression of a severity sufficient to provoke the individual to seek medical help. Precipitants may involve acute situations such as loss of a job, impending divorce, or more persistent disturbances of the social environment. The number presenting to a doctor for help will depend on many factors, but there is no doubt that publicity emphasizing the availability of treatment for depression encourages more to do so.

Many of these patients receive treatment with antidepressant drugs and show an improvement in mood. We have little information on the natural course of these minor disturbances of mood, and it is far from proved that there is any specific response to drugs. It is possible, however, that many such episodes are minor attacks of depressive illness.

Depression from Drugs

Mention should be made of "iatrogenic" depression, which may complicate the use of drugs for other unrelated conditions. Examples are the use of hypotensive agents such as α -methyl dopa, reserpine, and bethanidine, of corticosteroids, and of appetite suppressants such as fenfluramine. Withdrawal of the drug, when possible, or a change of medication may be followed by recovery from the depression, but in other patients further treatment of the depression will be required. Among these drugs are several which have important interactions with antidepressive drugs (see below).

TREATMENT IN GENERAL PRACTICE

A practical approach to the treatment of mild depression in general practice might be as follows. If the reaction seems appropriate, avoid prescribing drugs for a time, and if possible

see patients and relatives on several occasions to explore the situation. If the depression deepens or if the initial assessment indicates that the depression is inappropriate, a trial of drug therapy is indicated. A tricyclic antidepressant, as discussed below, should be given a thorough clinical trial. Both relatives and patients will benefit from an explanation of the nature of depressive illness and the aims of treatment. The explanation cannot be a standard one but must be matched to the intelligence and education of the patients. It should include a description of likely side effects of drug treatment—for example, with tricyclics drowsiness, dry mouth, and difficulty in visual accommodation—and also a clear indication of the latent period before response to treatment can be expected. Patients should be warned of the dangers of driving a car during the early period of antidepressant medication, when drowsiness is most pronounced. The potentiating effects of tricyclic drugs on the response to alcohol should also be stressed. This information will encourage patients to persist with the drug during the difficult early period, when they may for a time feel worse rather than better. If improvement occurs, then in general tricyclic antidepressants should be continued for a period of three months before an attempt is made to withdraw them.

If there is no response to a tricyclic drug after three to four weeks on adequate dosage a reassessment is necessary. New information may indicate that environmental precipitants are more important than originally thought, or an increase in the severity of the picture may indicate the need for a change of therapy.

It is important to stress to the patient that in most cases depression is a self-limiting condition and that even without drugs it will lift in time. This emphasis may help the physician to resist pressures from a patient to provide changing patterns of drug therapy in mild but drug-resistant depressive reactions.

Moderate to Severe Depression

The depressed patient is in a dependent position and he finds great difficulty in maintaining social contacts. He displays a lack of confidence and is self-critical. He often withdraws from attempts to cope with his environment and is particularly sensitive to further defeats even in minor matters. The therapist must be prepared to accept the patient's dependency and to give reassurance and explanation, which may provide a measure of temporary relief, though the effect is likely to be short-lived.

Severely depressed patients may require admission to hospital. In general the presence of delusions and of severe guilt feelings are an index of loss of touch with reality to such an extent that hospital management may be preferable. A history of suicidal attempts or strong suicidal thoughts also points to the need for admission. Social circumstances will often contribute to the decision for and against admission.

The choice of physical methods of treatment includes a drug and electric convulsion therapy (E.C.T.). In general E.C.T. is reserved for those patients in which drug therapy has failed or the acute case in which delay to await a drug response is not justifiable—for example, when there is a serious risk of suicide.

When drugs are prescribed the first choice is as for mild depression, one of the tricyclic group. For seriously agitated patients additional sedation may be required, and this is best achieved with a phenothiazine tranquillizer such as thioridazine (Melleril) 25-50 mg three times a day. Night sedation, if required, is best provided by nitrazepam (Mogadon). The administration of a large proportion of the tricyclic drug—for example, a 50-mg dose—before retiring may avoid the use of additional sedation.

Combined Anxiety and Depression

An attempt should be made to decide which of the conditions is primary. Depressive illness sometimes presents with anxiety

arising without adequate cause, often in the form of panic attacks. Treatment is by antidepressant drugs with monoamine oxidase inhibitors, which at times are more effective than tricyclic agents. There can be little justification for the use of blunderbuss preparations for treating both anxiety and depressive symptoms.

Tricyclic Antidepressants

There is a wide choice of drugs, but a few of these have considerably more evidence to indicate their efficacy than the rest. The author's choice would, in general, lie with one of the three compounds—imipramine, amitriptyline, and clomipramine.

Amitriptyline is more sedative than imipramine and is perhaps the drug of choice when agitation accompanies the depression. There are reports that cardiac arrhythmias may be more readily precipitated in elderly patients by this drug than by the other tricyclics, and hence it seems reasonable to avoid its use in the elderly or in those with known ischaemic heart disease. Treatment is begun with 25 mg three times a day in most patients, the dose being increased after a week to 50 mg three times a day if side effects are not too troublesome. A higher dose, up to 200 mg a day, may be tried in patients who fail to respond to the lower dose. In general, failure to respond in three weeks on 150–200 mg a day indicates the lack of a specific response. Studies of amitriptyline levels in serum have suggested that there is an optimal range within which improvement is maximum and that blood levels below and above this range are associated with less improvement. At 150 mg a day, however, it seems that most people will develop therapeutic blood levels, and for the time being we must judge our dose by the clinical criteria of response versus side effects, as blood level estimations are unlikely to be available as a routine procedure.

Imipramine may be of particular value for patients in whom depression is accompanied by marked retardation. The treatment regimen is similar to that for amitriptyline.

Clomipramine has certain pharmacological differences when compared to the other two drugs. While the others predominantly influence the re-uptake of the transmitters, noradrenaline and dopamine, clomipramine has a relatively greater effect on the uptake of 5-hydroxytryptamine. All transmitter systems are thought to be involved in the control of mood, but unfortunately we cannot specify the relative degrees to which they are so in different depressive syndromes.

At the clinical level clomipramine has been claimed to be particularly effective when obsessional and depressive symptoms coexist. In the author's experience it also seems to be worth a trial in patients who have not responded to the other tricyclics. Dosage is similar to that for the other two drugs, but since clomipramine has a greater tendency to produce postural hypotension than the other two the doses must be built up slowly, particularly in the elderly.

Side effects are rarely a serious problem with these drugs, but elderly men may suffer retention of urine, and occasionally nocturnal confusional states may develop. Drug combinations are dealt with in a later paragraph.

Monoamine Oxidase Inhibitors

The place of these drugs in the treatment of depressive syndromes is much less clearly defined than for the tricyclics. They may be particularly effective when anxiety accompanies depression. This interpretation of the situation is consistent with their reported value in the management of phobic anxiety and in atypical depression. The dangers of these drugs were perhaps overemphasized for a time, for if attention is paid to avoiding incompatible drug combinations they have a good, safe record.

Phenelzine is the author's choice in a starting dose of 15 mg three times a day. It is now known that the metabolism of this

drug by the liver is subject to genetic variation. Two groups of individuals can be distinguished, one group metabolizing the drug at a considerably faster rate than the other. Thus on 15 mg three times a day the rapid metabolizers do not have adequate drug levels. If there is no response after three weeks on the drug in the absence of side effects it is reasonable to increase the dose to 60 mg a day and then to a maximum of 75 mg a day.

Side effects include hypotension, oedema, blurring of vision, and dry mouth. The patient should be advised not to take the last dose after 5 p.m. as phenelzine has a mild direct amphetamine-like activity which may interfere with sleep if the drug is taken later in an evening.

Treatment of Recurrent Depression

Affective disturbances are recurrent illnesses with periods of complete remission. Frequent recurrences can be very distressing for patient and family alike even if the severity of the attacks is not very great. One example is the housewife who has episodes of depression every few weeks lasting for 10 days or so during which she feels lethargic, cannot cope with her family or her housework, and may retire to bed. In contrast we have the patient with recurrent attacks of severe depressive illness with months or years separating the attacks. In both types of patient the attacks are disabling and the morbidity high so that treatment which offers prevention of attacks relieves much suffering.

For recurrent depression in patients with no tendency to hypomanic swings, two treatments have been claimed to have preventive values. They are continuation of a tricyclic drug, such as amitriptyline, or the administration of lithium salts. Amitriptyline continued in a dose of 75–150 mg a day after recovery from an attack of depression has been shown to protect against further attacks in the subsequent 12 months.

Alternatively lithium is given in repeated doses as tablets of lithium carbonate (Camcolit) 250 mg or as a single daily dose of sustained release tablet (Priadel) 400 mg. The treatment is best regulated by regular plasma measurements, which at 12–18 hours after taking the ordinary tablets, and 12–27 hours after the sustained release preparation should be in the range of 0.8–1.2 mEq/l. Lithium is potentially a very toxic drug. Signs of toxicity appear at a plasma level of 1.5–2.0 mEq/l with tremor, drowsiness, and sometimes nausea and vomiting. Untreated, they may progress to stupor, with myoclonic jerking and epileptic attacks, and to a fatal outcome unless effective therapy is instituted.

Thus, while this is an important addition to the range of drugs available for the management of depression, it is vital to emphasize that starting a patient on lithium necessitates close follow-up and supervision. In most cases, therefore, it is perhaps appropriate that treatment for the time being should be concentrated in psychiatric units, many of which operate special lithium clinics.

NO MIRACLES

We are not clear at present about the most appropriate treatment for the mild recurrent depressions described above. But it is important to avoid any promise of "miracle" cures. A realistic approach which offers the individual some support without removing the need for an active contribution from patient and family is most effective. In the case of a wife it is unlikely that assessment will be complete until her husband has been interviewed. It is most typical in these mild recurrent depressives, irrespective of cause, that rearrangements have taken place within the family organization which may, in themselves, be perpetuating the disorder. For example, the wife's role may have been taken over by the husband as a result of her repeated periods of depression. Other factors such as isolation, sexual or financial difficulties in the marriage, and worries about children may be obvious precipitants.

However, none of these factors satisfactorily explain the

periodicity of the disability in these patients. In a few patients the periodicity may be accounted for by an exaggerated premenstrual syndrome or by the cyclic administration of an oral contraceptive drug. Such definite and potentially modifiable physical precipitants cannot be identified in most patients. For these, if it is decided that drugs are required, it may be reasonable to recommend a trial of a tricyclic drug, given in adequate dosage up to 150 mg a day through a period of several expected "attacks." A three-month trial will be long enough for most patients; if successful it may be continued on reduced dosage for a year. The plan should be spelled out to the patient, including the intention to withdraw the drug. Failure of this regimen should lead to a reassessment: Is this really a pathological reaction? Does this patient reject any sort of mood change? Is his tolerance for distress so low that he demands treatment for mood responses that others would regard as normal responses to life's stresses?

The total rejection of distress may be an increasing phenomenon in this age of widespread facilities for social support. It can be a dangerous diagnosis and not a very acceptable one to society at large. Certainly confrontation of the patient with the suggestion that he is overreacting is not a useful method of dealing with the problem, neither is it helpful to offer a passport to permanent happiness in the form of drug therapy. The physician must be sympathetic but firm. He must not venture an opinion prematurely but take time to listen to the patient and, if possible, to the relatives. The family doctor may already have valuable insight into the reactions of patient and family.

SECOND OPINION

Failure of the tricyclics to prevent these mild but troublesome episodes of depression should probably be an indication for a second opinion, usually a psychiatric opinion. It is valuable to have a clear statement of the treatment to date, including the dosage and duration of any treatments and also any relevant comments on the known situation.

It would then be appropriate to consider either further drug therapies treatment—for example, a trial of lithium carbonate or a monoamine oxidase inhibitor. Alternatively if there are indications that the patient might be helped to a more adaptive approach to life stresses a period of more formal psychotherapy might be suitable, and it might bring the husband and others into a family therapy approach. The dangers, which are often difficult to avoid, are that this entails a hospital takeover, with loss of the family doctor's assistance and delays in handing back the patient to his care. Unfortunately the successful co-ordination of G.P. and hospital treatment is apt to take more time than many of us can spare. Yet surely the long-term solution for these common mild depressives must be to shift the focus back to general practice.

At present nearly all the assessment of the potency of anti-depressant drugs is carried out on the selected (and presumably more severe) cases which present for hospital treatment, yet the bulk of the prescriptions are by family doctors for patients with mild or early depression. A critical evaluation of the value of drugs and perhaps other forms of treatments in general practice is long overdue.

Drug Interactions

The depressed patient often takes drugs for long periods of time, and so it is not surprising if he sometimes receives other drugs either to treat concurrent illness of a physical type or in an attempt to provide additional relief for his depressive symptoms.

Tricyclic antidepressants inhibit the uptake of catecholamines into postganglionic sympathetic nerve endings—for example, those in the walls of blood vessels and in the heart. The effect of drugs such as amphetamine and other sympathomimetics

which release noradrenaline at these nerve endings may be potentiated, with resulting hypertension and cardiac arrhythmias. The monoamine oxidase inhibitors which impair the inactivation of the noradrenaline may also result in potentiation, with occasionally serious consequences. What is perhaps surprising is that the combination of monoamine oxidase inhibitor and tricyclic is not more generally toxic. In fact the combination is recommended by some psychiatrists to treat cases of resistant depression. The answer is probably to be found in the choice of antidepressant. Amitriptyline is less likely to lead to increased sensitivity to released noradrenaline than imipramine, for its effect in inhibiting re-uptake is countered by a blocking effect on noradrenergic receptors. The use of a combination of monoamine oxidase inhibitor and tricyclic is probably best left to those with experience of it and should not be regarded as a first-line treatment.

Tricyclics have been shown to interfere with the actions of hypotensive drugs of the guanethidine—bethanidine series. Such a combination negates the blood-lowering effect of the hypotensive agent, the tricyclic effectively blocking its access to its site of action by inhibiting the process of uptake into sympathetic nerves.

The monoamine oxidase inhibitors now have a reputation for serious drug interactions which is perhaps at times overstressed. Sympathomimetics combined with them may give rise to hypertensive crises. Included here is the tyramine reaction, which results from the ingestion of foods containing the amine tyramine. Serious potentiation of drugs of the pethidine—morphine type may occur as a result of interference with their hepatic metabolism. Less known is the potentiation of insulin and hypoglycaemic agents, which may lead to hypoglycaemia if the dose of the drugs is not adjusted.

Treatment of Resistant Depression

Occasionally depressive illness persists despite all attempts at treatment and leads to a distressing situation for relatives and patients and to a frustrating situation for the physician. It is unlikely that an illness would be classed as resistant in under six months, as adequate trials of standard treatment taken in sequence would take this time.

A review of the situation should ascertain that when drugs have been used they have been given in adequate dosage for adequate periods of time. Before he is considered resistant to treatment a patient should have received a tricyclic antidepressant, a monoamine oxidase inhibitor, and at least one course of electric convulsion therapy. When this situation has been reached and the patient remains depressed, a complete re-evaluation is called for.

It should not be forgotten that the administration of anti-depressant drugs cannot guarantee the return of happiness. Even if there is a mechanism in brain where function is disturbed and which is returned to normal by drug treatment, the process of mood elevation may be prevented by adverse environmental circumstances. It is little use persisting with increasingly heroic treatments in a patient who has no reason to recover from his depression. Once again, therefore, a difficult clinical decision remains to be made: Is this patient still suffering from an illness requiring physical methods of treatment? If the answer is Yes, several possible lines of treatment are available. Drug treatment of resistant depression mainly consists in an attempt to potentiate the effect of existing drugs. It is impossible here to go into a detailed description of these treatments, but a few brief details may be noted.

The administration of a monoamine oxidase inhibitor together with a tricyclic agent (usually amitriptyline) is best left to an experienced psychiatrist, in whose hands it may carry little risk. Other treatments include the combination of the amino acid L-tryptophan (Optimax) and a monoamine oxidase inhibitor,

and the combination of a tricyclic drug with small doses of thyroxine or triiodothyronine; the latter treatment is said to be more effective in women than in men.

The use of prefrontal leucotomy in the treatment of severe cases of resistant depression is still a controversial subject. Certainly with the new stereotaxic operations personality change

is a less frequent complication of the operation. However, there is a reluctance to embark on an irreversible procedure in what is always a potentially reversible disorder. In weighing the prognosis against the possible disadvantages of the operation it is advisable to obtain the opinion of someone with considerable experience of it.

Contemporary Themes

Cost-benefit Analysis of Long-term Haemodialysis for Chronic Renal Failure

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British Medical Journal, 1975, 2, 376-379

Summary

A cost-benefit analysis of long-term maintenance haemodialysis indicates that there is a large gulf between the cost of the service and "economic" benefit. The difference may be considered to represent one estimate of the price society is prepared to pay to maintain life. Using "best estimates" from available data we found the implicit social value of maintaining a patient on haemodialysis to be approximately £4720 per annum in hospital or £2600 at home. The analysis would suggest that society must look carefully at alternative uses for health expenditure before extending indiscriminately to large sections of the population these treatment programmes or others similarly expensive.

Introduction

There are 46 units in the United Kingdom for the treatment of acute renal failure by long-term maintenance dialysis. This method of therapy has been expanded steadily in the past 10 years, and there are now about 580 patients being dialysed in hospital units and about 830 dialysing themselves at home.¹ A similar expansion of dialysis units has occurred in Western Europe, the U.S.A., and Australia. However, the number of patients taken on to the programme each year still falls short of the number considered suitable for long-term dialysis. Estimates of the incidence range between 23 and 39 new patients per year per million population under the age of 55-60.²⁻⁴ Though in the past it has been indicated that shortage of trained staff rather than direct economic constraints has held back provision of this form of medical care in the United Kingdom,⁵ maintenance dialysis does in fact have a high and continuous cost, and, even if staff shortages can be overcome, analysis is required to

examine whether the benefits from such therapies justify the use of the scarce resources involved.

In 1967 Kerr reported to the Royal Society of Medicine the very high cost of providing long-term maintenance dialysis to all potential candidates under the age of 55 in the U.K.⁶ In the United States Klarman, Francis, and Rosenthal made a cost-effectiveness comparison of hospital dialysis, home dialysis, and renal transplantation in terms of life years gained.⁷ Their approach was extended to a cost-benefit analysis by LeSourd, Fogel, and Johnston in a report prepared for the U.S. Department of Health, Education, and Welfare.⁸

Our paper adopts a similar approach, though it introduces an alternative means of expressing the results and incorporates several important differences regarding the data. Firstly, recent statistics from the European Dialysis and Transplant Association (E.D.T.A.)¹ are used as the basis for the estimates of relevant costs and benefits, supplemented by more detailed data from recent expenditures in Cardiff and Glamorgan. Secondly, adjustment is made for the fact that patients must first survive a period on hospital dialysis while training for home dialysis and waiting for installation of machinery and necessary home modifications.⁹ Omission of this led earlier studies to exaggerate the advantages of home dialysis over hospital dialysis by comparing the survival rates of patients on home dialysis with those on hospital dialysis. Thirdly, account is taken of the cost effects of the dependence of home dialysis patients on fully equipped hospital units and of costs incurred privately on nursing and special diets.

2. Patient Survival on Long-term Dialysis

The data for patient survival used in this analysis are those reported by the E.D.T.A. for the period ending 31 December 1972.¹ That survival has not improved as rapidly as many have hoped may be explained in part by expansion of the programme, so that each year there have been new, inexperienced units taking on initial and not typical cohorts of patients. However, this situation is likely to be repeated if the programme is further expanded. The six-year survival of patients on hospital dialysis was reported by E.D.T.A. as 50%. This is detailed in column 3 of table I. Our "best estimate" of long-term survival is based on an extrapolation of the E.D.T.A. survival data for years 1 to 6 inclusive fitted to a negative exponential function ($s = 1 - e^{-kt}$, where s is survival, t is time, and k is a constant; the correlation coefficient relating this function to the observed survival is

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