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DRUGS IN THE TREATMENT OF DEPRESSION*

BY

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When I began working in a large London general teaching hospital, after spending my earlier years in psychiatry at specialized psychiatric hospitals, I very soon started to realize that in the large numbers of treatable cases of depression being seen by general practitioners and physicians everywhere the diagnosis may be overlooked for long periods of time. These are not the severe cases of melancholia so easily recognizable by everybody and sent on early for specialized psychiatric treatment. They are the far more numerous patients with milder and more atypical depressive illnesses, sometimes diagnosed as anxiety states, many of whom get sent to general hospitals for all sorts of investigations because they complain of pains or other disturbances in almost every bodily organ. They, and often their doctors, think that their feelings of depression are caused by these bodily disturbances instead of being, of course, the other way round. What so often happens, after all tests and examinations are found to be normal, is that they are strongly reassured that there is nothing at all the matter with them, and nothing else is then done. And so they go away feeling just as ill and depressed, and even more hopeless than ever.

The fatal toll of suicides is mounting ever higher and higher in this country, so that over 5,000 people are now killing themselves annually. And large numbers of these are just such depressed patients who have already been seen by doctors and who have obtained so very little help from them that suicide seems the only way out of their problems and suffering.

This tragic state of affairs, however, coincides with the fact that depressive illnesses are now the most easily treatable and also have the highest potential for recovery of all types of mental illness. Patients can nearly always be helped out of an attack of depression, most of them fairly speedily, if only the correct diagnosis is made and the appropriate treatments are given.

Antidepressant Drugs

Most of you already know about older advances such as the use of electric shock, modified leucotomy, sleep, and modified insulin treatments in depressive states, but much less is known as yet about the proper use of what may well become another major advance in the treatment of the depressions—namely, the recent discovery of a whole new range of antidepressant drugs. And it does seem that these are now bringing to a large number of depressions of a certain type the possibilities

of easy and effective treatment by general practitioners and general physicians alike.

Now, drug manufacturers are aware—often much more so than many doctors—of the enormous number of patients with depression needing help, and with the advent of these new antidepressant drugs their advertising pressure upon us all has become very serious indeed. Just as happened when the new tranquilizers were introduced, foolish and absurd claims were made for their value in quite the wrong types of patient, so we are again seeing at the present time an intensive advertising of the new antidepressant drugs for cases of depression in which they may be quite unsuitable, and if used can only increase the grave risks of suicide always present in severe depressive illnesses. And because the chemical treatment of depression is now becoming such “big business,” each drug firm is trying to produce its own slightly different antidepressant drug, and sometimes claiming advantages over its equally and sometimes more efficient rivals, and altogether adding chaos to the present confusion about the real value of all these preparations.

Fortunately, at St. Thomas's we have for nearly three years been able to test, often in advance of their general use, many of these drugs, and they are being produced in still greater numbers and varieties. In fact, it is becoming difficult to cope properly with all of them, and some are being rushed on to the market, I am afraid, with very little testing indeed in this country (Dally and Rohde, 1961).

The general overall position about their uses and abuses is, I think, now becoming much clearer. Most of the advertising which suggests that these drugs are valuable in the treatment of depressions in general is not true; for most of them do not really help many of these patients, who are so obviously depressed that even the relatively untrained practitioner and general physician can see this immediately. In other words, the classical melancholic depressions—those depressions needing, and often being so quickly and certainly helped by, electric shock treatment—are far from being always helped by the new antidepressant drugs.

However, some evidence is accumulating which suggests that if electrical treatments are combined with the use of one or other of the appropriate antidepressant drugs, then sometimes the number of electrical treatments otherwise needed may be reduced. Also, some patients with severe depression respond to electric shock and then tend to relapse again quickly afterwards; and it also seems that if the antidepressant drugs are used after electric shock treatment has been stopped the

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relapse rate may not be as great. Furthermore, there are occasional patients with deep endogenous depressions who, after the failure of electric shock earlier on in an attack, do seem to be greatly helped towards the end of their attacks by the use of these new chemical agents. But it has not yet been possible, for instance, to show that the actual number of patients needing out-patient and in-patient E.C.T. at St. Thomas's has greatly lessened with the advent of the new antidepressant drugs, though we use them very intensively. Claims being made that these drugs are as effective as E.C.T. and can replace it are both misleading and dangerous.

Advantages of Antidepressants

Where, then, do the great advantages of some of the antidepressant drugs lie? Apart from those already mentioned, it is, paradoxically, in a group of depressions which have received practically no descriptive publicity or special advertising from the drug manufacturers. But they constitute a very much larger group of patients who are seen every day by general practitioners and psychiatrists alike, and who, up to recently, have often constituted a very difficult diagnostic and therapeutic problem for us all. They are what have been termed by West and Dally (1959) at St. Thomas's the "atypical" or "hysterical" types of depression, or they could alternatively be labelled as patients suffering from neurotic or reactive depressive illnesses or even sometimes from anxiety hysteria. Most of you will quickly recognize the sort of patient I mean when I describe them.

They are patients of *known good previous personality* who may have been through some special or prolonged stress or experienced a great shock. They have then suddenly or gradually become much more emotionally unstable. They have insight, and bitterly deplore the fact that whereas they used to be in control of their emotions, now their emotional moods have taken control over them. One day they are depressed or anxious, and the next day they may feel better again, often for no apparent reason at all. Unlike the true endogenous depressives, their sleep may not be much curtailed by early morning waking, but after a long night's sleep they say that they wake up just as fatigued and as tired as ever. Others complain of a poor quality of sleep, of disturbing dreams, and of general restlessness. General fatigue is also one of the symptoms of which they so bitterly complain, and they contrast their present tiredness and lethargy with their normal state, when they are usually most energetic and active people. It is this feeling of extreme fatigue which often stops them from coping with the simple daily duties that used to come so easily, and they may become fearful of the simplest tasks. Irritability also becomes exaggerated, and, unlike most true depressives, they blame others as well as themselves. Women in this group also complain frequently of severe premenstrual tension or depression. There may even be a marked hysterical exaggeration of symptoms when ill, though they are not hysterical people when well. And often, too, there has been a very considerable associated loss of weight.

Despite the fact that the patient is one who has usually faced up to the normal worries and problems of daily living, he has now ceased to be able to do so, and one often feels that he needs some sort of psychotherapy because he seems incapable of dealing with the environmental troubles that can beset us all at times.

And in the past this is what so often had to be suggested in the way of treatment, since little else helped them; left alone, many will gradually emerge spontaneously from their reactive depressive state with time, but their incapacity may last for months or even years.

Monoamine Inhibitors

Now, it is just these atypical or hysterically depressed patients with good previous personalities who, if treated with some of the new antidepressant drugs, may show such remarkable improvements even in the matter of a very few days. Iproniazid ("marsilid") is one of the most effective of this particular group of what are called monoamine-oxidase inhibitors, but the danger of a severe toxic jaundice in one in 250 patients makes it undesirable, except with special precautions and in those rare cases that should respond but are found quite resistant to all the other drugs now available in this group.

We have found phenelzine ("nardil"), 15 mg. t.d.s. to q.d.s., and isocarboxazid ("marplan"), 10 mg. t.d.s. to q.d.s., to be the most practical, efficacious, and safe amino-oxidase inhibitors for general use, though neither is as effective as iproniazid. We have not found nialamide ("niamid") to be as good as phenelzine or isocarboxazid in the cases described above; and, although pheniprazine hydrochloride ("cavodil") can be effective, yet its complications seem greater and can be more disturbing to the patient than the other two already mentioned. The most common complication of phenelzine, isocarboxazid, and others in this group is postural hypotension and the occurrence of giddiness or feelings of faintness on getting up or on moving quickly. This may mean having to lower the dose; and sensitivity differs from person to person. Finding the correct dose for each patient is very important because of the side-effects when too much is given. Fortunately, toxic jaundice has not yet been reported with the use of phenelzine or isocarboxazid as it has with iproniazid and pheniprazine.

If one is going to get a good result in these atypical depressions, it will generally start in the first week or ten days. Feelings of fatigue rapidly lessen, and patients again begin to face normal problems easily. Generally, improvement will start as early as the third or fourth day with this betterment in the feeling of fatigue; sleep may also improve (though it worsens in some patients initially), and feelings of tension also start to lessen. Sometimes there is a rapid switch-over to feelings of great well-being and, rarely, to actual hypomania.

In some cases the drug can be stopped as soon as the patient feels better again, but in most a rather longer period of maintenance treatment is needed, with a gradual tailing off after a month or so. Some more chronically depressed patients feel so much better on the drug, and so much worse when it is stopped again, that its use can be continued for months on end with obvious benefit. Relapse may start only two to three days after the drug has been stopped or lowered too much, and not immediately, and unless this is realized the relation between a relapse and the stopping of the drug may be missed. So far there seem to have been no undesirable complications with the prolonged use of these drugs, and addiction to increasing the dose is not acquired, since raising the dose produces unpleasant side-effects.

This same group of monoamine-oxidase inhibitors can also be used to try to prevent the recurrence of the

more neurotic types of depressive symptoms in patients who suffer from such periodic depressions. These drugs may be given in small doses all through the normal phase, and the dose increased as soon as the depressive phase comes on and until it lifts again. Before the introduction of these drugs there was no real means of helping such unfortunate patients, and even now we may not be able to stop the attacks in deeper recurrent depressions, only the depth of the attack being perhaps lightened or shortened.

Imipramine

Another of the new and widely publicized antidepressant drugs, imipramine ("tofranil"), is not an amino-oxidase inhibitor and is more closely allied to the chlorpromazine ("largactil") group of drugs. On the whole, it is far more effective in the more endogenous types of depression, but is of less value in the neurotic types of depression already discussed. It also generally takes longer to work. The dose needed may vary from 25 to 75 mg. t.d.s., and it can undoubtedly bring some of the milder cases of endogenous depression out of their attacks without the need for electric shock treatment; but one may have to wait for up to a month for this to happen, and in most cases of deeper endogenous depression E.C.T. is still desirable. To put deeply depressed patients on imipramine alone, and to leave them too long on it while awaiting possible improvement, may actually result in a marked worsening of symptoms and in what should have been a quite unnecessary suicidal attempt.

Imipramine can, however, be useful in helping to maintain recovery after the use of E.C.T. and in preventing future attacks. And, as already mentioned, there is now some evidence that the giving of imipramine during the course of E.C.T. may diminish the number of treatments otherwise needed; and this, too, applies to some of the monoamine-oxidase inhibitors, such as phenelzine and isocarboxazid. In cases in which there is doubt regarding which group of drugs is the most efficacious in a particular patient, one can sometimes combine, say, phenelzine and imipramine, and even give both of them together with E.C.T. Here, however, there is naturally a greater risk of postural hypotensive effects and other complications. But some patients do seem to tolerate quite large combined doses, such as imipramine mg. 25-50 t.d.s. and phenelzine mg. 15 t.d.s., very well indeed.

Outlook for the Future

What do all these advances mean for the future? Well, when I first entered psychiatry in 1934 there were no effective treatments of depression, and, just as now, psychotherapy was showing itself to be a most uncertain and very limited form of treatment in this large group of illnesses. But in the past twenty-five years one has seen what has amounted to a total revolution in treatment. Unfortunately, the training of medical students in the recognition of even such common psychiatric illnesses as simple depressions has been so deplorable because of the lack of time so often allowed in the medical curriculum that it will be impossible for some time to come for us to take full advantage of all the significant advances in treatment that have been made in recent years. However, if the various types of depressed patients can only be recognized early and distinguished one from the other by general doctors, numbers of neurotic depressions in people with good

previous personalities, and some endogenous ones as well, can now be quickly and effectively treated by the use of some of the new antidepressant drugs in the way I have described.

Other advances such as E.C.T., the provision of better and more varied types of long- and short-acting barbiturates, all the amphetamine drugs, the new tranquillizers, the use of modified insulin, and, when everything else has failed, a consideration of the most successful new and more modified forms of leucotomy—all such advances make the actual position to-day one in which there are very few cases of depression indeed, either acute or chronic, and occurring in good previous personalities which cannot be helped back to renewed efficiency and happiness in living. The skill, however, must still lie in the proper selection of patients for all the varied types of physical treatment now available to us, and a much longer paper would be needed to exhaust this whole fascinating and important topic.

Conclusion

I do believe, however, that all these recent physical advances in the treatment of depression also spotlight what must almost inevitably happen in most other major psychiatric illnesses in the years to come. For we are bound to discover more and more empirical physical methods of treatment to help them, and we shall also continue to learn more about their fundamental physiological nature and causes. I still remain quite unrepentant in my beliefs that a lot of our present-day specialized psychiatric and psychotherapeutic treatments will become more and more unnecessary in the future. And the next twenty-five years will see very many more of our patients able to go back and be treated quite simply and easily by the general practitioner and general physician using ordinary medical methods.

REFERENCES

- Dally, P. J., and Rohde, P. (1961). *Lancet*, 1, 18.
Sargant, W. (1960). *Psychosomatics*, 1, 14.
West, E. D., and Dally, P. J. (1959). *Brit. med. J.*, 1, 1491.

"ACUTE WHEEZY CHESTS"

CLINICAL PATTERNS AND NATURAL HISTORY

BY

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The management of the patient with a "wheezy chest" is a common problem in British medical practice to-day, as it has been for many centuries past. According to my own estimate and that of others (Goodall, 1958; Fletcher *et al.*, 1959), the family doctor in an average-sized practice (2,500) may expect to see in any year between 100 and 150 patients complaining of wheezing in their chests and shortness of breath, and of these some 40 to 50 will be seen for acute and distressing episodes of wheezing and breathlessness. It is these acute episodes that cause most of the troubles for the patient and most of the problems for the doctor, and it is with this group of cases that the present paper is concerned.

A non-specific term such as "acute wheezy chest" has been used on purpose rather than terms such as "asthma" or "bronchitis," because it was intended to study a clinical syndrome and not a specially delineated group such as "asthma."