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Psychotropic drugs

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Introduction

Of the many patients with psychological illness or disorders in which emotional factors are important, a large proportion are given psychotropic drugs. Many improve because of this treatment and some despite it. The potent agents now available are liable to produce side-effects or toxic effects which have to be set against the potential benefits conferred by these drugs. If drug treatment is appropriate the problem is to choose the compound most liable to produce beneficial effects—regardless of whether weight-for-weight it is the most potent drug—which also has the least risk of unwanted effects (Lader, 1967). This is clearly a complex matter and to gather sufficient information to make a reasonable choice requires both adequate trials to demonstrate the drug's clinical efficacy and sufficient clinical experience to discover the incidence and nature of the side-effects. In clinical trials of psychotropic drugs all the problems of spontaneous change, the effect of concurrent environmental changes, the patient's relationship to medical staff, the potential bias of patient and doctor, the difficulty of assessing subjective changes and of measuring relevant objective changes, demand a careful design to the trial if the results are to have any significance. It is also necessary to verify that the subjects are taking the medication under trial, for it has been found that among out-patients as many as 48% may not be taking the treatment prescribed (Wilcox, Gillan & Hare, 1965).

Many doctors have pointed out that in their hands various psychotropic drugs prove to be more successful than results published even in satisfactorily controlled trials. Although this may be partially accounted for by their better intuitive selection of appropriate patients for particular treatments, it may well be that faith plays a large part. Faith may well move mountains, and enthusiastic approach can help certain patients who have had no benefit from the treatment of more cautious therapists. Unfortunately, when it comes to proving that faith has actually moved the mountain, the peak often remains obstinately far away unless the distance is assessed by the fervent practitioner free to move about in the haze appropriate to the altitude. In these circumstances, clinical enthusiasm is an unreliable basis for pharmacological knowledge or subsequent hypothesis.

Periodic reviews of the toxicity of psychotropic drugs report unwanted side-effects, e.g. over-sedation, hypotension, or extra-pyramidal disorders, dangerous allergic responses, e.g. agranulocytosis, and toxic effects, e.g. liver necrosis or acute hypertension (Hollister, 1964). There are also the dangers of addiction and overdose. In any one year in Great Britain, each of the more popular drugs used in the treatment of anxiety, depression or schizophrenia is quite likely to feature in at least a million prescriptions. Even if the dangers are relatively infrequent, there are bound to be a number of occasions when drug toxicity will cause a patient (or the relatives) and the doctor to doubt if the original prescription was really justified. This clearly means that even familar drugs should not be prescribed without due consideration and to do so is to incur an unjustifiable risk. Moreover, if a popular sedative or anti-depressant drug is unthinkingly prescribed before making adequate enquiry into the patient's life, a potentially alterable cause of the emotional distress may be neglected. Unfortunately, it must be confessed that frequently the causes of psychiatric disorders are indeterminate or the circumstances so unfavourable that immediate radical cure is unlikely. In such cases the symptomatic relief which medication can provide is often a most useful alternative or accessory treatment.

Sedatives

Drugs which allay anxiety have been widely used and during the last few decades doctors have been able to prescribe some very effective

sedatives, notably the barbiturates. Such is the established position of the barbiturates that there is now a useful custom of selecting amylobarbitone sodium as a standard for comparing other sedatives or tranquillizers in the same way that quinalbarbitone or pentobarbitone act as a comparison for newer hypnotics. The pharmacological basis of their sedative action remains unclear. Barbiturates depress brain activity in a number of ways. This has been shown at a metabolic level in experiments that have measured the reduced oxygen uptake of active brain tissue exposed to barbiturates (McIlwain, 1966). In electrophysiological work, the brain-stem reticular system has shown itself to be particularly sensitive to barbiturate action, although its effect is by no means limited to this (Brazier, 1965). The relationship between these metabolic and electrophysiological changes and the reduction of anxiety is still far from clear, although there may be some connection between the level of arousal in terms of brain activity and the features of anxiety.

Owing to some of their disadvantages the barbiturates are no longer such an automatic first choice to sedate anxious patients—there is also a swing of opinion due to a discontent that leads to the use of other sedatives, not because they are better, but because they are different. The disadvantages of barbiturates include drug dependency, where repeated ingestion results in tolerance, reduced therapeutic benefit and social problems. Not a few patients, often those with some inadequacy of personality, find it very difficult to stop taking the drug once it has provided partial relief from chronic emotional distress. More serious addiction is not rare, patients demonstrating an impairment of concentration, co-ordination or consciousness from time to time. Barbiturate withdrawal is liable to cause an anxiety state, fits or delirium on withdrawal not unlike that other sedative, alcohol (Isbell & Frazer, 1950). The problem more frequently encountered in hospital is the acute intoxication from an overdose, often taken impulsively by desperate people who can find no solution to their problems (Kessel, 1965). A large majority of such patients recover consciousness with conservative treatment, although further measures may assist drug excretion in the seriously intoxicated person (Geall, 1966). Their further outlook depends on the extent to which their social situation or their personal adaptation to life improves, which it may do following the social upheaval following the self-poisoning or as the result of deliberate social and psychiatric treatment.

A drug to alleviate anxiety as effectively as the barbiturates without the risks of impaired concentration, allergic responses and the dangers of repeated or excessive dosage would be very welcome. None of the recently marketed drugs have proved to be that excellent in spite of initial optimism. Drugs used to relieve anxiety include compounds which require an arbitrary judgement to separate sedatives from tranquillizers. In this article meprobamate (Equanil), tybamate (Solacen), etc., and the benzodiazepines which include chlordiazepoxide (Librium), diazepam (Valium) and nitrazepam, (Mogadon) will be included under the heading of sedatives as they can impair concentration and performance in the doses commonly used and they also have some hypnotic value. It is recognized, however, that these drugs do not act in an identical fashion to barbiturates and some may prefer to regard them as tranquillizers (any logical distinction between so-called minor and major tranquillizers has, so far, eluded me). In particular the benzodiazepines and meprobamate do not show the selective effect on the brain-stem reticular system that characterizes barbiturates; and they do have a remarkable effect in taming animals which are ferocious either as a consequence of their nature, their circumstances or experimental lesions of the brain.

Both the benzodiazepines and meprobamate have survived the initial stages of exaggerated claims, resultant criticism and the disappointments that ensue when unwanted effects are reported. They are quite widely used today and so far there are fewer records of serious effects of overdose than with barbiturates. This may be due both to a greater margin of safety and more infrequent resort to these agents for suicidal attempts. A considerable number of controlled trials have now been published and although some of these have failed to find any significant difference from placebo, many of them report findings that meprobamate, chlordiazepoxide and diazepam have a therapeutic effect (Jenner, 1965) One comparative trial of chlordiazepoxide and amylobarbitone sodium with a placebo was of particular interest in that it showed the value of both drugs for anxious patients but could show no significant difference between them when using a number of physiological and clinical measures (Lader & Wing, 1965).

Tranquillizers

Phenothiazines

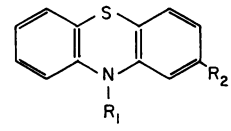
Chlorpromazine soon made its mark when introduced into psychiatry in the early 1950s. It was clear that the phenothiazines held thera-

peutic promise because of the actions of compounds such as promethazine which was not only an antihistamine, but also a sedative and had the power of potentiating anaesthetics. Chlorpromazine was also found to have many actions and these included the property of calming anxious or agitated people. Its ability to do this without necessarily altering the level of consciousness to any great extent led to its recognition as a very valuable clinical 'tranquillizer'.

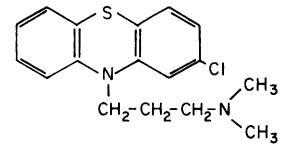
This desirable achievement aroused great pharmacological curiosity which has not yet been assuaged by an adequate explanation. There is evidence that chlorpromazine influences a number of enzyme systems including interfering with oxidative phosphorylation (Richter, 1965) but the link between its metabolic effects and clinical action is obscure. Chlorpromazine antagonizes adrenaline in various animal experiments and, to some extent, it also opposes the action of acetylcholine, histamine and serotonin. Quite possibly its antagonism to biogenic amines in the brain accounts for some of its depressant actions. Its depressant effect would be expected to be more selective than ordinary sedatives, and this is confirmed as regards the brain-stem reticular system. Electrophysiological work shows differences between chlorpromazine action at this level and that of the barbiturates which produce a marked general reduction of the responsiveness of the brain-stem arousal system. Chlorpromazine depresses the reticular system sensory input which comes through collateral branches from the main afferent pathways, but this drug does not greatly alter the responsiveness of the reticular system to direct electrical stimuli. Chlorpromazine given to cats in doses that do not produce general sedation will potentiate normal habituation, i.e. reduce responsiveness to arousal responses and to conditioned stimuli, whereas in experiments without chlorpromazine the conditioned responses habituate more slowly. This effect of enhancing habituation to conditioned stimuli may well have intriguing links with the drug's clinical tranquillizing action (Bradley, 1963).

With chlorpromazine's success a number of other phenothiazines followed. The basic phenothiazine structure is shown in Fig. 1, with substitutions at the R_1 and R_2 positions. The R_2 substitutions are simpler, often a halogen, methyl or methoxy group, which affects the potency of the compound. Common substitutions at the R_1 group are dimethylamine, piperazine and piperidine side-chains and these three types form convenient groups for clinical consideration. Examples are shown in Fig. 1.

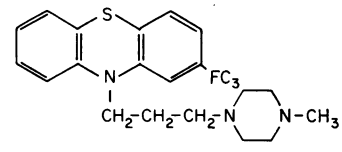
The clinical actions of the dimethylamine group are typified by chlorpromazine, still a very popular drug. It has now been amply proved that this drug can bring about a great improvement in patients with acute schizophrenia. One study of 400 acutely ill patients showed that 75% of those taking phenothiazines, including chlorpromazine, showed marked or moderate improvement in 6 weeks compared with only 23% of those receiving an inert preparation (N.I.M.H. Group, 1964). Although 'tranquillizers', chlorpromazine and similar compounds in larger doses will sedate and cause drowsiness. This impairment of consciousness is much less than that brought about by therapeutically equivalent doses of barbiturates and so chlorpromazine is often useful in restless patients who are confused or suffering from withdrawal of addictive drugs. It also has its uses in anxious patients.



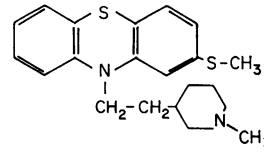
Basic phenothiazine structure



chlorpromazine (dimethylamine side-chain)



trifluoperazine (piperazine side-chain)



thioridazine (piperidine side-chain)

FIG. 1. Structural formulae of phenothiazines.

Having so many actions chlorpromazine is bound to have side-effects, some of which are disadvantageous. These include drowsiness, hypotension and Parkinsonism. Until recently it was confidently stated that the extra-pyramidal side-effects were temporary phenomena which would vanish when the dose of phenothiazines was reduced or stopped; but now a few cases have been reported of persistent abnormal movements of face, tongue and jaw following prolonged phenothiazine treatment (Hunter, Earl & Janz, 1964).

Chlorpromazine can produce idiosyncratic toxic effects in some patients. At one time it appeared that jaundice might occur so frequently as to seriously limit the value of the drug, but its incidence is not so high as to prohibit the use of this compound. When jaundice does occur it is of a cholestatic type with the clinical and biochemical picture of obstructive jaundice, but without any signs of extra-hepatic obstruction, of course; it can easily prove a diagnostic pitfall. Fortunately this condition is usually benign (Cook & Sherlock, 1965). Idiosyncratic responses include skin eruptions and some individuals become exceedingly sensitive to the drug, often exhibiting a photosensitivity as well. The prolonged taking of phenothiazines for 2 or 3 years can produce deposits in the lens, cornea and the skin (Mathalone, 1965), and although no serious ill-effects are apparent the question has been raised whether widespread tissue deposits of a phenothiazine metabolite may do more than discolour skin. Occasional sudden deaths have occurred in patients receiving phenothiazines and it has been suggested that the drug could affect the tissues of the heart (*Lancet*, 1965). Another important type of drug reaction is the blood dyscrasias. Although they are not common in terms of the percentage of cases among people taking phenothiazines, as these drugs are used a great deal they probably account for many of the cases of agranulocytosis diagnosed and, less often, for some other blood-cell disorders.

The piperazine group of phenothiazines, such as perphenazine (Fentazin) or trifluoperazine (Stelazine), has some slightly different qualities from the dimethylamine group. These compounds are far less likely to produce drowsiness and this is an advantage in apathetic, chronically ill patients in whom further sedation is one more deterrent to useful positive action. They, with the piperidine group, are frequently given to patients who have developed paranoid schizophrenic symptoms later in life and their considerable success in reducing symptoms enables many patients to continue life in their normal community (Post, 1966). They are more potent drugs than chlorpromazine and less likely to produce skin, liver or blood-cell damage. They do tend to cause more in the way of extra-pyramidal symptoms, however, both in degree and type. Patients taking piperazine phenothiazines can exhibit, in addition to the common Parkinsonian rigidity, a motor restlessness, dystonic crises, and muscle contractions which can appear quite bizzare. These side-effects usually respond to anti-parkinsonian drugs.

The last group of phenothiazines to be considered here is the piperidine group, for example thioridazine (Melleril). Its potency is similar to chlorpromazine, but it does seem considerably less likely to cause toxic effects—except that retinal changes have been reported in patients taking large amounts of the drug. Thioridazine has a considerable sedative effect.

There has been considerable dispute over the questions of whether phenothiazines do more than calm schizophrenic patients and whether it is wise to continue giving phenothiazines over long periods. There is evidence that phenothiazines do more than reduce excitement and anxiety. In a comparison of chlorpromazine, fluphenazine (Moditen), thioridazine and a placebo, the drugs were shown to reduce apathy, motor retardation, indifference to surroundings, grimacing or giggling and self-neglect (Goldberg, Klerman & Cole, 1965). They also, in comparison with a placebo, lessened the likelihood of further symptoms developing. The use of phenothiazines to prevent relapse has considerable justification, of course, but this policy has probably led to much unnecessary treatment (Hughes & Little, 1967). A large proportion of patients having long-term phenothiazine treatment could stop it with no untoward effects. Investigations into the consequences of exchanging phenothiazines for placebo in patients who have previously required hospital treatment for schizophrenia have given varying relapse rates, and the not infrequent negative results have led some workers to protest against the unnecessary use of drugs. In one thorough study, however, the relapse rate was as high as 45%, and attempts to distinguish any particularly susceptible groups met little success (Caffey *et al.*, 1964). Clearly, no general rule can be applied concerning continued administration of phenothiazines to schizophrenic patients; most doctors gradually reduce the dose when it seems propitious to try.

There is no doubt that phenothiazines have been of great value in psychiatric treatment, but

this should not lead to blind faith in the drugs, especially in view of the side-effects and toxic effects that can arise. Together with reserpine, chlorpromazine and the later phenothiazines have given many people a renewed impetus to help patients with schizophrenia return to a normal or more normal life. The drugs have not been the sole cause of this advance, however, and attention to social and personal circumstances have played a great part in the improved prognosis of schizophrenia (Hordern & Hamilton, 1963).

Haloperidol

Haloperidol (Serenace) is often employed in the same circumstances as phenothiazines, that is for patients with manic and acute schizophrenic symptoms. Many regard it as the drug of choice for mania. Its side-effects, notably extra-pyramidal disorders which are often of a dystonic or dyskinetic nature, resemble those of the piperazine group of phenothiazines. It is often necessary, therefore, to administer orphenadrine (Disipal) or benztropine methanesulphonate (Cogentin) concurrently. In spite of the similaritities in clinical effects, haloperidol is not a phenothiazine but has the dissimilar structure of a butyrophenone. Again, like phenothiazines, it has been used with analgesic drugs to produce a state when a patient, although conscious, can undergo some operative procedures, indifferent to discomfort. Haloperidol and some more recently produced butyrophenones appear to have serious toxic effects only rarely. The basis of their action is uncertain, but like gamma aminobutyric acid (GABA) they may reduce the excitability of dopaminergic neurones.

Lithium

The use of lithium carbonate for manic illness was first suggested in 1949 but it did not become widely used because of its dangers and the difficulties of proving its value in a variable illness like mania. Serious risks, especially to the kidney, were encountered more when lithium was used as a sodium substitute (Schou, 1957). In psychiatric practice drowsiness, tremor and ataxia are warning signs of lithium intoxication and it is as well to keep the serum lithium level below 2 mEq/l. With such a regime mania is often controlled (Maggs, 1963). It has also been claimed that lithium improves depression and may relieve the recurrent mood-swings of manic-depressive psychosis.

In view of the changes in body sodium that have been described in affective disorders, the influence of lithium in this respect has aroused considerable interest. Using radioactive isotopes, Coppen and his co-workers (1965) reported that the residual sodium (intracellular and exchangeable bone sodium) fell when patients recovered from depression; similar changes appeared to occur in mania. It seemed from one investigation that giving lithium to such patients increased the exchangeable sodium, probably at the expanse of the residual sodium, but a recent study has failed to confirm this (Coppen & Shaw, 1967).

Anti-depressants

Although sedatives, notably alcohol, with their central nervous system depressant action, can give rise to euphoria, it is only in the last few years that some drugs have been used because they specifically relieve depressions of mood. Sedatives and tranquillizers relieve anxiety and agitation in depressive conditions but do not appear to have as great an effect on the depressive symptoms, although there is evidence that some of the phenothiazines such as thioridazine or perphenazine may have a mild anti-depressant action (Overall *et al.*, 1964; Hinton, 1959). The anti-depressant drugs of current importance fall into two groups; those characterized by their action of inhibiting monoamine oxidase (MAO) and those, like imipramine (Tofranil), with a tricyclic structure.

Monoamine oxidase inhibitors

The variety of laudatory and condemnatory reports about these drugs asserting either their efficacy in depressed patients or the risks of dangerous toxicity attending their use still leaves their use in dispute. There is no doubt, however, that the links between their pharmacological and therapeutic action have great theoretical value.

The first drug of this group observed to have an anti-depressant action was iproniazid (Marsilid) when it induced euphoria in some patients in whom it was tried as a treatment for tuberculosis. Although iproniazid did not prove to be as successful as isoniazid against the infection, it continued to be used for its psychotropic action and is not without its advocates today. The empiric use of the drug was soon linked with its action of inhibiting MAO. Iproniazid was found to increase the brain serotonin (5-hydroxytryptamine) in some animals. This seemed to provide a neat contrast with reserpine which depletes the stores of serotonin in the brain, depresses activity in animals and can sometimes depress the mood of man to a suicidal level. Moreover, there is some evidence that in the treatment of depressed patients giving trypto-

phan, a precursor of serotonin, can potentiate the therapeutic action of MAO inhibitors (Coppen, Shaw & Farrell, 1963).

Other mono-amines besides serotonin are involved when MAO action is blocked. The growing evidence now suggests that the catecholamine changes induced by MAO inhibitors may be more significant clinically. In various animal species the excitatory action of MAO inhibitors seems to be more closely linked to brain noradrenaline than serotonin Kety, 1966); but the complexities of monoamine metabolism in the brain and the recognized problems of extrapolating from metabolic and behavioural experiments in animals to man warn us against undue certainty about the way in which these drugs act (Holtz & Westermann, 1965). It is likely that the storage of monoamines in the tissues, including that of noradrenaline in the brain, is in a granular form protected from metabolizing enzymes. On nerve stimulation, noradrenaline is released and has its local effect before being re-stored or inactivated by enzymes. The enzyme acting on noradrenaline released from nerve-endings is probably catechol-O-methyl transferase. Mono-amine oxidase probably exerts its action in the vicinity of the tissue pools of stored catecholamines, inactivating them at that point if released, before they can exert a physiological effect. In spite of the generous amounts of MAO in the brain, the drugs are such effective blockers, that they are well able to inhibit 85% or more, at which point the brain content of mono-amines rises (Pletscher, 1966). It has even been possible to measure the 5-hydroxytryptamine content in the brain stem of patients who have died while taking MAO inhibitors and the serotonin level has been found to rise after 2 weeks of such treatment (Maclean *et al.*, 1965).

As would be expected, the discovery of a drug that could relieve depression in a novel way was shortly followed by a number of similar compounds, accompanied by reports of toxic effects and second thoughts about the therapeutic efficacy of the various compounds. Many of this group, for example, phenelzine (Nardil), nialamide (Niamid) and isocarboxazid (Marplan), like iproniazid, contained the N:N bond of hydrazine. The hydrazine MAO inhibitors are liable to produce hypotension and other side-effects, but more serious is the liver damage they occasionally inflict, isoniazid having the worst reputation for this. This toxic effect results in a condition which resembles virus hepatitis histologically and clinically; it can be fulminant and its mortality rate, once jaundice develops, has been reported to be as high as 25% (Cook & Sherlock, 1965). The controlled trials of these hydrazine MAO inhibitors have not maintained the earlier enthusiasm. Although some trials have shown that they do have an anti-depressant effect, and some workers have declared that these agents have a particular value in certain cases of depression characterized by anxiety features (Sargant & Dally, 1962), the evidence is not overwhelming. The M.R.C. (1965) investigation into treatment of depression failed to show any significant therapeutic difference between phenelzine and placebo.

A non-hydrazine inhibitor of MAO, tranylcypromine (Parnate) has been used widely, especially as some patients appear to get earlier relief from depression with this compound than with other MAO inhibitors. It has the advantage of not being hepatotoxic. Its particular hazard is to give rise to severe hypertension, whereas the hydrazine MAO inhibitors more often cause hypotension. The stimulant action of this drug could well be related to its similarity in structure to amphetamine (see Fig. 2) and, indeed, the early anti-depressant effect may be due to an amphetamine-like action. The hypertensive attacks often cause patients to experience a sudden severe headache, palpitations and other acute symptoms which may prostrate them in a manner not unlike that of subarachnoid haemorrhage —and occasionally there has in fact been such a haemorrhage.

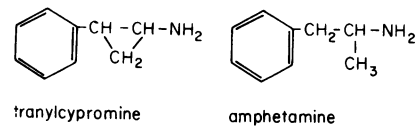


FIG. 2. Structural formulae of tranylcypromine and amphetamine.

Evidence has been gathered that these hypertensive episodes are largely due to monoamines in the diet which, owing to the very effective inhibition of MAO by tranylcypromine, are absorbed into the bloodstream and not metabolized in the usual fashion (Blackwell *et al.*, 1967). The significant monoamines are tyramine which is found in some cheeses, yeast extract and some alcoholic drinks, histamine which is found in yeast extract, and dopa which is present in broad beans. These can all cause unpleasant or dangerous effects. Since this knowledge became available in 1963, patients taking MAO inhibitors, particularly tranylcypromine, should have been warned to avoid these particular items in their diet. In one enquiry this simple measure

proved sufficiently effective to reduce the incidence of hypertensive crises in patients taking MAO inhibitors from 8·4% to 3·3%, and most of the 3·3% had disregarded the warning (Bethune *et al.*, 1964). The treatment suggested for such crises is 5 mg phentolamine intravenously. Besides the unwanted effects from dietary amines, synthetic amines such as methedrine can have a disastrous effect. Other drugs can have untoward actions once MAO has been inhibited. Pethidine can cause muscle spasms, pareses, pyrexia and coma.

The occurrence of unwanted effects with occasional fatalities and the relative lack of adequate clinical trials have made many people chary of using tranylcypromine, especially as a drug of first choice in depressed patients. The position has not been made any clearer by the fact that many automatically combine the treatment with trifluoperazine. Nevertheless, tranylcypromine is still favoured by many doctors as some depressed patients appear to respond quickly to this drug and some trials have reported its success (Atkinson & Ditman, 1965).

Tricyclic compounds

At about the same time that the MAO inhibitors were introduced into psychiatric practice, imipramine was also being prescribed as an antidepressant. Its iminodibenzyl structure is very similar to the phenothiazines, with a CH_2—CH_2 group in place of the S atom (see Fig. 3). Animal work had originally suggested that its clinical use would be as a tranquillizer but Kuhn (1958) observed that patients were often relieved of their depressive symptoms. Following the success of this compound as an anti-depressant there have been further modifications in the central structure to produce other tricyclic compounds and, of course, the side chain has also had its modifications. The structures of one or two frequently-used derivatives are shown in Fig. 3.

Explanations have been advanced to explain the anti-depressant effect of imipramine in terms of its pharmacological action on the monoamines in the brain. In animals imipramine can prolong the action of noradrenaline (Holtz & Westermann, 1965). Imipramine does not inhibit MAO, however, and does not alter the level of brain amines. It has been suggested that the drug interferes with the normal rebinding and inactivation of noradrenaline when released at the nerve endings. Imipramine may alter the membrane permeability at this site, increasing the activity of noradrenaline at the receptor site (Klerman and Cole, 1965). In animal experiments it has been shown that imipramine is metabolized and, by losing a methyl group, becomes desipramine (see Fig. 3) an active agent. Given to rats desipramine sensitizes the adrenergic receptors to the action of brain catecholamines especially when they are released by reserpine-like substances (Brodie, 1965). Such theories regarding the pharmacological relief of depression in man, however, must remain speculative as long as the relevant metabolic accompaniments of lowered mood are not established.

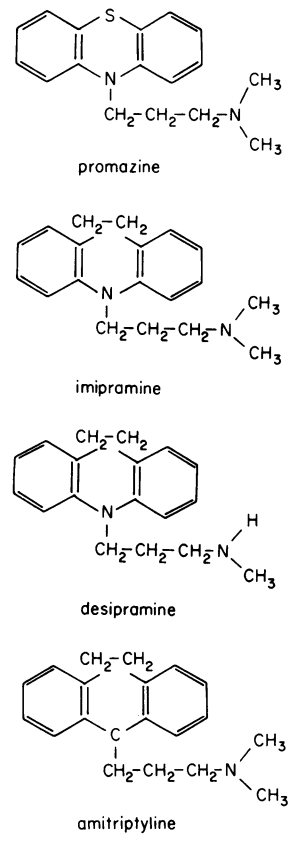


FIG. 3. Structural formulae of a phenothiazine and some tricyclic anti-depressants.

Owing to their lower toxicity and greater therapeutic efficacy the tricyclic anti-depressants are usually prescribed more readily than the MAO inhibitors. Serious toxic sequelae are uncommon, although the side-effects of these drugs can occasionally be so troublesome as to limit their use. The disturbance of the autonomic system induced by these drugs can cause patients to experience dryness of the mouth, increased

sweating, disturbed accommodation, constipation and dysuria. Tremor, unsteadiness, alterations in cardiac rate or rhythm and hypotension also occur. As the pharmacological actions of these drugs would lead one to expect, giving them concurrently with a MAO inhibitor could possibly lead to an excessive brain stimulation, resulting in tremors, sweating, vascular collapse and hyperpyrexia. Nevertheless, a few physicians make a practice of using the MAO inhibitors and tricyclic anti-depressants together in a powerful pharmacological brew, which they justify on the grounds that depressive illness itself endangers life and that the theoretical risks of the treatment are rarely encountered in practice. The tricyclic compounds are not hepatotoxic in the manner of hydrazine MAO inhibitors; cholestatic jaundice and agranulocytosis, which occur with the related phenothiazines, are uncommon sequelae to treatment with tricyclic antidepressants.

There is greater conviction about the relief of depression by the tricyclic compounds than MAO inhibitors. The majority of controlled trials have shown a significant difference from placebo although a few have not. Anti-depressant agents have to bear comparison with electroconvulsive therapy (ECT) an accepted effective treatment for severely depressed patients, but a treatment that requires a skilled team to avoid any unnecessary anaesthetic or other risks, and even when well administered may prove an unpleasant procedure for some patients besides giving some a temporary memory disturbance. The early controlled studies of imipramine by Kiloh and Ball (Ball & Kiloh, 1959; Kiloh & Ball, 1961) showed its effectiveness and indicated that although depression might not be relieved so promptly with the drug as with ECT, continued treatment with imipramine could reduce the chances of relapse. These findings are similar to the careful M.R.C. trial of treatments for depression (1965). It is generally held that an adequate dose of imipramine of 150–200 mg daily may take 1–3 weeks before the therapeutic effect becomes apparent. In the M.R.C. trial, after 4 weeks' treatment 39% of those on the placebo had lost all symptoms (emphasizing the need for controls in such experiments) while 52% on imipramine and 71% receiving ECT were well. On being followed up 6 months later, the difference in the outcome between patients treated with imipramine and ECT had gone, both treatments resulted in a little over half the patients remaining well.

This trial also indicated that imipramine is more effective in men than women. When attempts are made to find particular forms of depression responsive to particular anti-depressants, the evidence is contradictory; this is only to be expected while it is quite unclear if there are separable forms of depressive illness. It is often said that imipramine relieves 'endogenous' depression more often than 'reactive' depression but in addition to the difficulties of distinguishing the types this comparison is not as simple as it sounds; if, for instance, the circumstances to which a person is reacting persist, it will make it difficult for any drug to produce a contented mind. Attempts to relate clinical features of the illness to a favourable outcome with imipramine have often been disappointing (Fleminger & Groden, 1962). A report from the United States showed that some depressed patients with anxious or phobic features responded well to imipramine (Klein, 1964) whereas this seems very like the group of patients which some workers in Britain say responds particularly well to MAO inhibitors. Attempts have been made to distinguish those responding to MAO inhibitors from those responding to tricyclic compounds and relating this to genetic aspects of the individual (Pare, Rees & Sainsbury, 1962). Although this approach holds greater theoretical promise than the disappointing attempts to delineate syndromes of depression susceptible to particular drugs, the results are as yet inconclusive.

Other related compounds now compete with imipramine as the anti-depressant drug of choice. With the discovery of the part played by desipramine as an active agent in rats given reserpine, it was hoped that using desipramine (Pertofran) might shorten the period taken by imipramine before the effects of treatment became apparent. Unfortunately this hope has not been borne out to any clinically significant extent, and in depressed people imipramine seems to be the more useful drug (Edwards, 1965). A slight change in the central structure of imipramine has produced amitriptyline (see Fig. 3), a compound which has proved to be of considerable clinical value. Controlled trials by Hordern and fellow workers (Burt *et al.*, 1962; Hordern *et al.*, 1964) have compared amitriptyline and imipramine, and shown the former to be better in some respects. Other comparative trials of amitriptyline have also found it equal or superior to imipramine (Hoenig & Visram, 1964).

Amitriptyline is similar in therapeutic effect and side-effects to imipramine. It is more likely to make patients drowsy, but this is sometimes an asset in patients with depressive agitation or

insomnia—imipramine can worsen insomnia. Hordern, reviewing the treatment of depression (1965) noted that if depressed patients do not begin to improve in appetite, sleep, work and interests within a week of starting amitriptyline, they are likely to require other treament. As with imipramine, the incidence of relapse with drug maintenance is lower over a 6-month period than it is after ECT although, in appropriate cases, ECT initially has greater success.

Nortriptyline (Aventyl) and protryptyline (Concordin) have a similar central structure to amitriptyline but with further modifications to the side-chain so that (parallel to desipramine) they are desmethylated forms. There is as yet less clinical evidence concerning these drugs than for amitriptyline, but the evidence available for nortriptyline appears favourable and protriptyline may well prove useful.

Amphetamines

These drugs are unlike the anti-depressants in that they can stimulate normal people when tired and they do not appear to have a specific effect on depressive illness. Amphetamines alone have not been very useful in the treatment of depression, but in combination with barbiturates they have had a disquieting popularity. Perhaps, with the problems of drug dependency and occasional cases of amphetamine psychosis, present-day reluctance to prescribe amphetamine–barbiturate mixtures has meant sacrificing the potential benefits of short-term use of such drug combinations (Hare, McCance & McCormick, 1964). This sort of loss, however, applies to many drugs which have defects as well as considerable merits; and the defects of amphetamine misuse have proved to be serious.

Psychotomimetic drugs

Psychotomimetic (or psychedelic or psycholytic drugs) have not gained an established place in psychiatric treatment but they have their enthusiastic advocates and they are of considerable heuristic interest.

These drugs such as lysergic acid diethylamine (LSD) produce striking mental changes involving dramatic alterations of perception and of mood. The mood changes are often pleasurable with a mystical component, but they can be terrifying. Such effects have been used in the treatment of various neurotic conditions and personality disorders, including alcohol addiction. Therapeutically LSD has been administered with the intention of making the patient more readily aware of material from the unconscious which is utilized in the psychotherapeutic process. It is also used for its psychedelic value, in the expectation that the intense drug-induced experiences will help throw off crippling inhibitions or disturbing patterns of behaviour through a conversion to a new set of values and a better adjustment to life. Clearly if altering the boundaries of consciousness or mental experience are to be beneficial, the experiment is best conducted in an environment where any long-lasting changes that may eventuate are towards an improved adjustment to society rather than the contrary. Some workers, using LSD, have helped some patients with chronic disorders to make remarkable improvement, and have attributed the change to the use of the drug (Hoffer, 1965). A few workers in this field become remarkably enthusiastic about such treatment and it almost seems that their own psychedelic experiences have led to their spurning the more cautious traditional scepticism with which others view such therapeutic claims. Although it is difficult to manage a closely controlled trial of such treatment, at least one comparison of LSD therapy with adequate conventional treatment of patients with neurotic problems has not shown the drug to improve the outcome (Robinson *et al.*, 1963).

The use of psychotomimetic drugs, be they LSD, mescaline, psilocybin, psilocyn, *N,N'*-dimethyltryptamine (DMT) or other compounds, is not without complications. There are the social issues involved in repeated resort to the drugs, and the occasional adverse psychological responses to the drugs such as a prolonged mental disturbance or an acute distress which has led to suicide (Faillace, 1966). Recently some evidence has been discovered to show that LSD and related drugs may alter chromosomal structure, a potentially sinister finding (*Lancet*, 1967).

The fact that drugs can produce abnormal mental states which have some resemblances to schizophrenia has prompted a number of theories about the nature of their pharmacological action and the aetiology of mental illness. Some of these drugs have a resemblance to normally occurring catecholamines and serotonin; mescaline, for instance has a similar basic structure to noradrenaline (see Fig. 4). Perhaps a disturbance of a metabolic process such as methylation could cause a biochemical upset manifested by psychological changes. In the past few years the significance of various toxic or abnormal substances which have been described as present in the serum or urine of schizophrenic patients has been widely debated and currently the role of dimethoxyphenylethylamine and the 'pink spot' have been discussed and disputed (Smythies,

1967). As yet none of the reports of abnormal metabolities described as occurring in schizophrenics have been wholly accepted but in spite of past disappointments the promise remains.

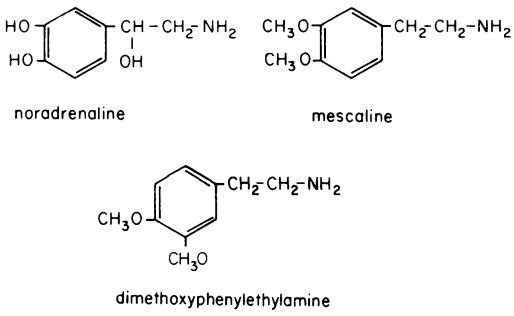


FIG. 4. Structural formulae of some amines relevant to hallucinogens and, possibly, schizophrenia.

Conclusion

The available knowledge concerning psychotropic drugs is now vast, but very far from complete. Assumptions and inadequate data lead to fashions of treatment many of which may, in retrospect, prove hard to justify. In the absence of a satisfactory understanding of the action of psychotropic drugs, it is not easy to fit new knowledge into a unifying pattern nor to summarize the present position. A chapter on recent advances in this field, which contained 951 references, included the comment that we now need reviews of reviews (Siminoff, 1964). The present review is brief, patchy, presumably biassed and bound to be out of date in several respects. This warning is meant to convey an implied apology, together with an appreciation of the continuing growth of pharmacological and therapeutic knowledge on which one aspect of psychiatric treatment is based.

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