INDICATIONS FOR THE USE OF DRUGS IN THE TREATMENT OF PSYCHIATRIC DISORDERS

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DURING the past decade the drug treatment of psychiatric illness has advanced with remarkable rapidity.

The principal drugs concerned are those with predominant actions on higher mental and neurological functions and collectively referred to as psychotropic drugs. The main drugs used in practice can be classified into

- (1) Anti-psychotic drugs (Neuroleptics).
- (2) Anti-depression drugs.
- (3) Anti-anxiety drugs.

The harbingers of the modern era of pharmacotherapy in psychiatry were reserpine and chlorpromazine.

Reserpine was rediscovered after use by Indian physicians many hundreds of years ago and chlorpromazine was first used by Laborit in France to facilitate low temperature surgery because of its suppressive action on the central and peripheral parts of both divisions of the autonomic nervous system. Later, chlorpromazine was used by Deniker, Delay and other members of the French school of psychiatry for treating psychiatric illnesses.

Major Tranquillizers (Neuroleptics) *Alkaloids derived from Rauwolfia serpentina*

These include reserpine, deserpedine and rescinnamine.

They have a depressant action on hypothalamic structures and the reticular system, which is intimately concerned in determining degree of alertness. The effects of reserpine are tranquillization and reduction of activity. It differs from chlorpromazine in its autonomic effects as it stimulates parasympathetic activity producing side effects such as bradycardia, nasal congestion, dyspepsia and diarrhoea. It also differs in the time taken to produce therapeutic effects which may take as long as six weeks to develop. After a preliminary sedative phase, lasting 10 days or so, there follows a stage of 'turbulence' lasting for

some three weeks which is then succeeded by an integrative phase when the patient becomes more co-operative, interested and friendly with relief of symptoms.

Reserpine and related alkaloids are valuable in controlling overactive and disturbed behaviour in schizophrenia and other psychiatric disorders, but have now been superseded for this purpose by the phenothiazine drugs which produce clinical effects more quickly and reliably.

A serious complication of reserpine therapy is the development of a severe depressive state which may carry the risk of suicide and may need electroconvulsive therapy.

Tetrabenazine is a new synthetic drug with an action similar to reserpine. There is some evidence that it may be of value in treating chronic schizophrenia.

Phenothiazine Derivatives

Table 1 lists the most commonly used phenothiazine derivatives. They are mainly in three groups: (1) the dimethylamine series, (2) the piperidine series and (3) the piperazine series. Differences in chemical structure, which are mainly achieved by substitutions at R₁ and R₂, are associated with marked differences in potency, clinical activity and toxicity.

Substitutions at R₁. Three main side chains are concerned as substituents at R₁:

- (1) Dimethylamine.
- (2) Piperidine.

TABLE I

Generic Name	Trade Name(s)	Daily Dosage (mg.)		Side-effects				Toxic and Hyper-sensitivity Effects				Principal Indications	Limitation and Disadvantages
		Low	High	Autonomic	Behavioural Effects	Extrapyramidal	Hypotensive	Seizures	Liver Pathology	Blood Dyscrasia	Edema		
1. <i>Dimethylamine series</i> Chlorpromazine	Largactil Thorazine	75	1,000	+	+	+	+	+	+	+	+	Overactivity, disturbed behaviour in schizophrenia. Acute and chronic organic mental state (mental defectives and disturbed children).	Little use for anxiety states. Limited value for inert and apathetic schizophrenia.
2. Trifluopromazine	Vespral	20	150	+	+	+	+	+	+	+	+	As above.	As above.
3. Lævo-promazine	Verachi	25	700	+	+	+	++	+	±	±	+	As above — greater sedative action.	Markedly hypotensive.
4. Prothipendyl	Tolnate	40	120	o	±	o	±	o	o	o	±	Anxiety states. To facilitate sleep by its sedative action or to potentiate hypnotics.	Value in schizophrenia not established.
5. <i>Piperazine series</i> Prochlorperazine	Stemetil Compazine	15	100	+	+	+	+	+	±		o	Vomiting, tinnitus, prevention of migraine. Schizophrenia, including inert and apathetic patients.	Dystonic reaction in higher doses.
6. Perphenazine	Fentazin	6	64	+	+	+	+	+	±	±	+	Schizophrenia. Disturbed behaviour in psychiatric and physical disease.	Dystonic reaction in higher doses.
7. Thio-propazate	Dartalan	15	150	+	+	+	±	+	o	±	o	Schizophrenia acute and chronic. Overactive disturbed behaviour in all psychiatric disorders. Management of Huntingdon's chorea. Little or no danger of liver damage.	More effective and safer than chlorpromazine.
8. Flu-phenazine	Moditen Permtil Prolixin	0.5	10	+	+	+	+	±	+	+	+	Mainly for preventing anxiety and tension.	Extrapyramidal side-effects frequent.
9. Trifluoperazine	Stelazine	3	30	+	+	+	±	+	±	±	o	All types of schizophrenia. Low doses for anxiety symptoms.	Extrapyramidal side-effects frequent.
10. <i>Piperidine series</i> Pecazine	Pacatal	75	400	+	+	o	o	o	+	+	o	Relief of tension and anxiety in neuroses. Reports on therapeutic efficiency are conflicting.	Side-effects more unpleasant than chlorpromazine.
11. Thioridazine	Melleril	30	600	+	+	+	+	+	+	+	+	As tranquilosedative in neuroses and psychoses.	Side-effects frequent.

- (3) Piperazine. This side chain gives increased potency but a greater tendency to increased alertness and to induce extrapyramidal phenomena.

Substitutions at R₂ are mainly by such radicals as halogens, methoxy and methyl groups.

The presence of a chlorine atom is directly related to the tendency to produce jaundice in chlorpromazine. Promazine carries no danger of jaundice but is only one third as potent as chlorpromazine. Fluorine, on the other hand, conveys higher potency than chlorine.

The various phenothiazine derivatives differ in clinical effects such as their potency in achieving tranquillization and sedation and their effects on alertness. They all potentiate the effects of central nervous system depressants such as alcohol, anaesthetics, hypnotics, sedatives and narcotics. In varying degrees they are anti-emetic, antihistamine, hypotensive, vagolytic and sympatholytic.

The piperazine derivatives are of higher potency than chlorpromazine and have greater tendency to promote alertness but also a greater tendency to produce extrapyramidal side effects.

Side-effects, toxic and hypersensitivity reactions. It is necessary to distinguish side effects from toxic and hypersensitivity reactions. Side-effects can occur in everyone if the dose is increased sufficiently but toxic and hypersensitivity reactions only affect a proportion of persons and their occurrence is not closely dependent on dosage.

Chlorpromazine

Chlorpromazine has a variety of interesting pharmacological effects and clinical applications. It is a central nervous system depressant with little action on the cerebral cortex but selective actions on certain cortical structures and on both central and peripheral parts of the autonomic nervous system. It has hypotensive, sympatholytic, vagolytic and weak antihistamine activity, as well as anti-emetic properties, and potentiates the effect of sedatives and narcotics and anaesthetics.

Chlorpromazine has stood the test of time and is a reliable drug for the treatment of disturbed behaviour, tension and excitement and overactivity in schizophrenia, hypomania and in organic mental states, such as senile dementia, arterio-sclerotic dementia, etc. in mental defectives and in children with behaviour disorders. Its value in neuroses is limited and it is of little value in the treatment of depressive states apart from the relief from some degree of tension and anxiety. In normal and neurotic patients it tends to produce too great a feeling of apathy and indifference and its action in relieving anxiety is variable and unpredictable.

Anti-depression Drugs

There are three main groups of drugs used for elevation of mood:

- (1) Central nervous system stimulants, amphetamines, pipradol and methyl phenidate.
- (2) Monoamine oxidase inhibitors.
- (3) Imipramine and chemically allied drugs.

Central Nervous Stimulants

The really important advance in the pharmacotherapy of depression occurred with the discovery of iproniazid and imipramine some 4 to 5 years ago.

Prior to this the only agents available were the stimulants which had very limited application and serious disadvantages.

The main indication for the amphetamine drugs is in patients with short-lasting, early morning depression of moderate or mild degrees of severity.

The disadvantage of amphetamines includes tolerance, dependency and addiction. Short-lasting elevation of mood is followed by post medication increased fatigue, irritability and depression.

Monoamine oxidase Inhibitors

The finding that reserpine which sometimes causes depression produces a fall in levels of noradrenaline and serotonin in the central nervous system and that iproniazid raises their level with concurrent increased psychomotor activity, provided a stimulating hypothesis for research workers on biochemical and pharmacotherapeutic aspects of depression.

The work of Kline revealed the value of iproniazid in treating depressive illnesses. Iproniazid has a serious disadvantage in causing toxic liver necrosis in some patients which not infrequently proved fatal.

A large series of new monoamine oxidase inhibitors have subsequently been discovered and used for treating depression.

Some of these have already been withdrawn because of toxic effects. The three which have stood the test of time are phenelzine, nialamide, isocarboxazid and tranylcypromine.

None of these drugs is as effective as ECT for severe endogenous depression. They are mainly of value for depressive illnesses of mild or moderate severity. Data on these drugs are given in Table 2.

Imipramine and Other Drugs

Imipramine is an iminodibenzyl derivative similar in chemical structure to chlorpromazine. Little interest was at first taken in this drug as its tranquillizing properties were slight and it was only when Kuhn demonstrated its value

TABLE 2

Generic Name	Trade Name	Usual Daily Dosage Range (mg.)	Autonomic Reactions	Hyperflexion	Hypertension	Hepatic Pathology	Blood Dyscrasia	Peripheral Edema	Other Effects
Iproniazid	Marsilid	5-75	+	+	+	+	+	+	
Phenelzine	Nardil	15-75							
Nialamide	Niamid	35-300	+	+	+	+	+	+	
Isocarboxazid	Marplan	10-30	+	+	+	+	+	+	
Tranlycypamine	Parnate	10-30	+	+	+	o	o	o	Severe headaches occasionally occur.
Imipramine	Tofranil	25-150	+	+	+	+	+	+	Parkinsonism and skin disorders may occur.
Amitriptylene	Tryptyzol	25-150	+	+	+	o	o	o	Dyskinesia and skin disorders may occur.

treating depression that its potentialities were recognized. Published reports in the main agree regarding its value in endogenous and reactive depressions. It is not as effective as ECT for the severe endogenous depressions.

The mode of action of imipramine is not freely understood. It is not a monoamine oxidase inhibitor, and does not produce excitation in normal subjects or animals.

Recent studies have provided evidence that the anti-depressive action of imipramine is probably mediated through a metabolic product, viz. a monomethyl analogue. The removal of a methyl group from imipramine results in greater rapidity of anti-depressant action.

Amitriptylene is claimed to be effective in relieving anxiety, tension and agitation and associated depression. Published reports are conflicting regarding its therapeutic value in depressive illnesses.

Anti-anxiety Drugs

These may be classified into:

- (1) Minor tranquilizers.
- (2) Tranquilosedatives.
- (3) Hyposedatives.

Minor Tranquilizers are central nervous system depressants acting on subcortical structures in diencephalon and midbrain but less marked and more discriminate in action than the major tranquilizers.

The main groups of minor tranquilizers are:

- (1) Phenothiazine derivatives such as promazine, promethazine and diethazine.
- (2) Benzhydryl derivatives including captodiamine and hydroxyzine.

Promazine is one-third as potent as chlorpromazine but does not carry the risk of jaundice.

It is useful in the management of alcoholic disorders as it does not affect liver function and has calming and anti-emetic actions. It is less hypotensive than chlorpromazine and preferable for treating those elderly people who tend to have syncope with hypotension and postural changes. It also has a place in management of mildly anxious or disturbed ambulant patients attending out-patient clinics or in general practice.

Hydroxyzine has adrenolytic, anticholinergic, anti-emetic, anti-histaminic and anti-spasmodic properties.

Its main use is relief of anxiety, tension and overactivity in neuroses.

Captodiamine has anti-histaminic, anti-emetic and some sedative effects. Clinical trials have failed to establish its therapeutic value as a tranquilizer.

Tranquilosedatives differ from the tranquillizing drugs in having no significant action on the autonomic nervous system. They are central nervous system depressants acting on polysynaptic spinal pathways. Extrapyramidal symptoms do not occur and in contrast to major tranquilizers they increase the threshold to convulsions.

Meprobamate was developed from myanesin, a muscle relaxant. Its main use is the treatment of neuroses for relief of anxiety and tension, particularly when associated with increased muscular tension.

When given in high doses over a long period tolerance and withdrawal symptoms may occur and therefore the risk of addiction.

Methaminodiazepoxide (Librium) has calming

properties without inducing sleep. It is anti-convulsant and a muscular relaxant and stimulates appetite. Its main indications are in neuroses for the relief of anxiety, distress, phobias and symptoms due to increased muscular tension.

It is also given with antidepressants to alleviate anxiety associated with depression. A number of new derivatives, analogues of Librium, have been produced and some are promising but not yet on the market.

Hypnosedatives

These are depressants of the cerebral nervous system which reduce spontaneous activity and which in large doses produce ataxia leading to hypnosis and in higher doses still, anaesthesia. They are used as hypnotics and some in lower doses as daytime sedatives.

Among the barbiturates amylbarbitone in doses of $\frac{3}{4}$ to $1\frac{1}{4}$ grs. three times daily is reliable and

effective for the relief of anxiety and tension. Among non-barbiturate hypnosedatives, glutethimide is a safe hypnotic and daytime sedative.

Methyl pentynol is effective in allaying apprehension in a variety of situations. Toxic reactions are frequent and consist of drowsiness, ataxia, dysarthria, diplopia, nystagmus and tremors. The carbamate derivative has longer duration of action and less toxic and side effects.

Conclusions

The discovery of new drugs in the past decade has revolutionized psychiatric treatment. Further advances can be expected. The need for careful testing and screening and fully controlled clinical trials before new drugs are marketed is at last becoming recognized and, when fully implemented, will accelerate progress in this important field of treatment for the most distressing illnesses which afflict mankind.