Clinical Pharmacology of Antipsychotic Drugs

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Antipsychotic drugs are widely used to treat abnormal behaviour particularly that related to the functional psychoses such as schizophrenia. This review discusses the pharmacokinetics and pharmacology of antipsychotic drugs like chlorpromazine. Clinical use comprises the induction of tranquillization in disturbed psychiatric patients, the treatment of acute and chronic schizophrenic symptoms, and the postponement of relapse in such patients. Unwanted effects are multifarious, involving many systems of the body. Extrapyramidal signs and symptoms are particularly noticeable, and the chronic type, tardive dyskinesia, is a major problem.

KEY WORDS: Psychosis; schizophrenia; antipsychotic drugs; extrapyramidal signs.

HISTORY

The parent compound of antipsychotic drugs, phenothiazine, was synthesized in the late nineteenth century and was used in the 1930s as a veterinary anthelminthic. A derivative, promethazine, has antihistaminic and sedative effects and, in the search for other antihistaminics, chlorpromazine was synthesized. Its antihistaminic properties are weak but it has powerful sedative properties in anaesthesia and surgery, inducing ‘artificial hibernation’ with tranquillization, marked unconcern and indifference to surroundings and to injuries, and lack of temperature control, combined with retention of consciousness and mental faculties. Psychiatrists tried chlorpromazine in manic and then other psychotic patients, and the unique combination of sedation and antipsychotic activity, without clouding of consciousness, was quickly recognized.

Quite soon, other phenothiazines were synthesized, developed and marketed. Most were piperazine side-chain compounds, such as trifluoperazine and fluphenazine, or piperidine-type compounds like thioridazine. Chlorpromazine is usually termed an aliphatic phenothiazine. In the 1960s, a new type of formulation was developed for fluphenazine in which it was coupled to a long-chain fatty acid and injected, in an oily medium, as a long-acting depot preparation. Several other similar compounds were introduced later.
The thioxanthenes are closely related chemically and pharmacologically to the phenothiazines. The butyrophenones are phenylbutylylpiperidines and have antipsychotic actions and a pharmacological profile similar to those of the piperazine phenothiazines. More recent developments have been the diphenylbutylpiperidines, such as pimozide, and the substituted benzamides, such as sulpiride.

About the same time as chlorpromazine was introduced, interest developed in the rauwolfia alkaloids, in particular, extracts of Rauwolfia serpentina. These substances had long been used in Hindu traditional remedies for several conditions including insanity. Reserpine, the principal alkaloid, was used for a while as an antihypertensive agent and as an antipsychotic. It was rapidly discarded as an antipsychotic agent, however, because a phase of increased disturbance usually preceded its therapeutic effects and because retarded, depressive reactions were sometimes induced.

Many other compounds have been synthesized in the search for new and improved antipsychotic drugs. In particular, the need for effective antipsychotic agents that did not induce extrapyramidal effects led chemists and pharmacologists to seek drugs with selective actions on the limbic system without effect on the basal ganglia.

**PHARMACOKINETICS**

Interest has focused on the prototypal compound, chlorpromazine. It is, however, metabolically complex: well over 150 metabolites have been suggested of which nearly 100 have been detected in blood or urine. Some metabolites are psychotropically active. The metabolism of other phenothiazines, such as thioridazine and flufenazine, is also complex but butyrophenones, such as haloperidol, and thioxanthenes, such as flupenthixol, seem less complex in this respect.

Plasma antipsychotic drug concentrations were initially measured using chemical methods and, later, radioimmunoassays. That these drugs bind to dopamine receptors has been exploited to develop radioreceptor assays, with the potential advantage that all substances in the plasma, drug and active metabolites, should be measurable. Unfortunately, the technique has yielded data which have been difficult to interpret.

**Absorption and metabolism**

Chlorpromazine and other antipsychotic drugs are very lipid soluble, and generally rapidly and completely absorbed. Much of the chlorpromazine and, possibly, other phenothiazines are metabolized 'first-pass' in the gut wall and liver after absorption. Intramuscular injections of either regular or long-acting formulations obviates this first-pass metabolism. Haloperidol and pimozide undergo relatively little first-pass metabolism.

After absorption antipsychotic drugs pass to the brain where they tend to accumulate. Chlorpromazine is metabolized by sulphoxidation, hydroxylation, N-oxidation and demethylation, these processes often succeeding each other. Eventually metabolites of low lipophilicity are produced or conjugates are formed and are excreted through the kidney. The sulphoxide is an important inactive metabolite. Patients who respond poorly to chlorpromazine have high levels of the sulphoxide while those who respond well have high levels of chlorpromazine or its unconjugated hydroxy metabolites.

Thioridazine is metabolized by sulphoxidation on the ring sulphur to form an inactive metabolite. Sulphoxidation on the thiomethyl substituent, however, results in active metabolites, including mesoridazine. Piperazine phenothiazines are metabolized much as is chlorpromazine, sulphoxide formation being the most important. The piperazine ring in the side-chain may be opened and further metabolites formed.
Thioxanthenes are metabolized similarly although hydroxylation does not occur. Haloperidol is split into two probably inactive moieties. The long-acting depot preparations are metabolized by splitting of the ester bond joining the parent drug to its long-chain fatty acid by aliphatic esterase enzymes. The parent drug is slowly released and absorbed from the injection site into the systemic bloodstream.

**Plasma concentration and clinical response**

Chlorpromazine has a fairly short elimination half-life (about 8 h) in plasma so that fluctuations in plasma drug concentration following each dose are appreciable. Concentrations of drug in the brain, however, may fluctuate much less because of the high lipid solubility of the compound. Other phenothiazines also have fairly short half-lives but some diphenylbutylpiperidines have such long half-lives that they can be given once weekly.

Following acute doses of chlorpromazine, psychiatric patients were sedated while plasma concentrations were high. Both very high (>500 ng/ml) and very low (<10 ng/ml) concentrations were associated with poor response. A further complication is that chlorpromazine induces its own metabolism by an effect on liver enzymes. Thus, plasma concentrations peak after 1–2 weeks of treatment and then decline to half or less over the next month.

For these various reasons it is hardly surprising that correlations between plasma concentrations and clinical response have been low and non-significant, although generally positive. In acutely psychotic patients, antipsychotic drug concentrations, as measured by a radioreceptor assay, tend to be either high or low in non-responders. Low levels are a weak predictor of relapse in chronic schizophrenics. Correlations with side-effects have also been sought: extrapyramidal syndromes are more common in patients with high plasma drug concentrations than in those with lower levels. Thus, at present, plasma antipsychotic drug concentrations do not usefully predict response in psychotic patients but may have limited usefulness in special situations, such as drug toxicity and overdose, apparently inexplicable resistance to drug treatment and idiosyncratic responses.

After stopping chlorpromazine, the drug rapidly becomes undetectable in plasma, as predicted from its short half-life. Due to its lipophilic nature, however, it tends to remain in organs with a high lipid content for some time and to be detectable in metabolite form in the urine. Clinical relapse may also be delayed.

The pharmacokinetics of depot preparations are still poorly detailed, mainly because of the technical problems of measuring their low plasma concentrations.

**Drug interactions**

Chlorpromazine can increase the metabolism of other drugs and, in turn, be metabolized more rapidly in the presence of other drugs, such as phenobarbitone. The antiparkinsonian drug, orphenadrine, reduces chlorpromazine concentrations in the body by inducing liver microsomal oxidizing enzymes. Cigarette smoking may also be associated with induction of liver enzymes and lowering of chlorpromazine drug concentrations. Conversely, some other compounds, for example steroids, oestrogens and, perhaps, tricyclic antidepressants, may compete with chlorpromazine for sites on liver enzymes and elevate chlorpromazine levels.

**PHARMACOLOGY**

**Biochemical pharmacology**

Almost all antipsychotic drugs induce extrapyramidal syndromes. The observation that giving antipsychotic drugs increased the turnover of the dopamine metabolite, homovanillic acid, prompted
Carlsson to postulate that these drugs block dopamine receptors thereby inducing a compensatory increase in the synthesis of dopamine. Dopaminergic blockade also accounts for the extrapyramidal effects, shown by antipsychotic drugs, in inhibition of the vomiting centre thus exerting an antiemetic effect, and interference with the control of growth hormones and prolactin release leading to decreased growth hormone levels and increased prolactin levels.

The affinity of various antipsychotic drugs for the dopamine receptor can be measured by their ability to displace radio-labelled haloperidol or a more potent derivative, spiroperidol. This can now be measured in man using positron emission tomography. Close correspondence between this property and clinical potency has been claimed. Affinity to muscarinic receptors can also be assessed: thioridazine has high affinity whereas chlorpromazine has moderate and haloperidol low affinity. The likelihood of extrapyramidal effects appears to increase proportionately.

Dopamine receptors may vary in their characteristics in different parts of the brain and some investigational drugs act preferentially in one or other region. So far, however, drugs have not been marketed for which the evidence is clear that mesolimbic and mesocortical dopamine receptors are blocked at concentrations which leave the basal ganglia unaffected.

Reserpine and its synthetic analogue, tetrabenazine, prevent the storage of amines in the granular vesicles of the pre-synaptic neuron. Dopamine, noradrenaline and 5-hydroxytryptamine are all affected so the antipsychotic action cannot be attributed to alterations in the disposition of any amine.

**Basic pharmacology**

The animal pharmacology of chlorpromazine correlates well with its biochemical effects. Dopamine receptor blockade accounts for a powerful anti-emetic effect; a screen for new antipsychotic drugs was the prevention of apomorphine-induced vomiting. Release of prolactin secretion is responsible for a lactogenic effect in animals and other endocrine effects reflect hypothalamic actions. Extrapyramidal effects manifest themselves as a general reduction in motor activity with diminished motor responsiveness and animals maintain unnatural positions in which they are placed, so-called 'catalepsy'. A more specific test involves the production of lesions on one side of the basal ganglia of rats. The animal runs round in circles and this behaviour can be blocked by giving antipsychotic drugs.

The anticholinergic effects of chlorpromazine and thioridazine, such as contraction of the guinea-pig ileus, can be measured using isolated tissue preparations. Anti 5-hydroxytryptamine actions for example on the rat uterus, can also be shown. Although chlorpromazine was originally developed from promethazine, its antihistaminic activity is quite weak. Anti-adrenaline properties are often marked. In the dog, chlorpromazine produces vasoilation by blocking adrenergic vasoconstrictor impulses, followed by a reflex tachycardia. A decrease in cerebral blood flow occurs but oxygen uptake by the brain is not affected.

**Neuropharmacology and behavioural pharmacology**

Collateral input from sensory pathways to the cortex is attenuated by antipsychotic drugs, lowering the throughput of impulses and consequent diffuse activation of the cortex. Antipsychotic drugs apparently have little direct effect on the cortex. Although dopaminergic pathways have now been traced to the orbital and cingulate cortices, blockade by antipsychotic drugs does not produce obvious effects.

Chlorpromazine increases sociability in
cats and decreases their hostility. This ‘taming’ effect can be seen in rhesus monkeys which are normally aggressive. Aggregated mice are made overactive by amphetamine and, subsequently, die; isolated mice are much less susceptible. Antipsychotic drugs prevent this toxicity.

Antipsychotic drugs markedly alter learning processes. The conditioned avoidance response involves the coupling of a warning signal with a noxious stimulus, such as footshock. Rats learn to avoid the noxious stimulus when the warning occurs. Antipsychotic drugs suppress this conditioned avoidance response without affecting the unconditioned response, namely jumping away after the footshock.

**CLINICAL PHARMACOLOGY**

The effects of antipsychotic drugs on human psychological functions are multifarious and complex. In addition to their primary antipsychotic actions, secondary effects on alertness and other mental functions are very obvious. For example, chlorpromazine is sedative as well as antipsychotic, whereas trifluoperazine and flupenthixol are somewhat stimulant. Tolerance to the acute sedative effects of chlorpromazine can be demonstrated. The antipsychotic effects of chlorpromazine and related drugs, however, persist after acute sedative or stimulant effects have worn off and are of prime clinical interest: these cannot, of course, be demonstrated in normal individuals.

Antipsychotic drugs have characteristic effects on the electroencephalogram—slow wave, $\theta$ and $\alpha$ activities are increased, whereas fast activity is decreased. Paroxysmal activity may increase and epileptic fits are more likely.

The autonomic effects of antipsychotic drugs are predictable from their animal pharmacology and easily demonstrated: postural hypotension, reflex tachycardia, stuffy nose, blurring of vision, lowered bowel motility and pupillary constriction.

**CLINICAL USE**

*Tranquillization*

Chlorpromazine was first used to help manage manic patients but it quickly became evident that disturbed behaviour, of whatever causation, responded to this agent. Previously, the drugs used to quieten noisy, combative and destructive patients were bromides, barbiturates, paraldehyde and opiates such as morphine and papaveretum. The drawbacks of these agents are that an initial phase of increased excitation might be induced due to release of the patient’s inhibitions; somnolence might supervene to the point of deep sleep and even coma; toxic confusional psychoses might be produced obscuring the clinical situation and complicating the diagnosis; and withdrawal syndromes might be precipitated or drug dependence initiated. The advantages of chlorpromazine in these various respects were so overwhelming that it quickly supplanted the existing sedatives. Thus, there is no paradoxical excitation, no clouding of consciousness, excessive drowsiness or danger of drug-induced psychosis, and dependence and abstinence phenomena are unknown. Despite expressions of distaste for this ‘chemical straitjacket’ as it has been stigmatized, antipsychotics remain the treatment of first choice in admission wards throughout the world. Their beneficial effects can be quantified quite simply and operationally in terms of the decrease in numbers of windows broken, hours patients spend in seclusion, assaults on staff and use of restraint: in many institutions the padded cell and the straitjacket have become museum pieces.

An important additional factor is the increase in confidence of the nursing staff in dealing with disturbed patients. The effectiveness of antipsychotic drugs can be substantially enhanced by firm, purposeful handling of the patient which knowledge and experience of the general effectiveness of the drugs usually produces.
The indications for the antipsychotic drugs in this non-specific role are accordingly wide. Freyhan, many years ago, drew attention to these diffuse indications, pointing out that chlorpromazine was effective mainly against symptoms related to hypermotility, abnormal initiative and increased affective tension, features which he dubbed 'target symptoms'. He listed the following indications for such symptomatic treatment. (a) Schizophrenia: states of restlessness and excitement, paranoid tension, panic and aggressive outbursts; stereotypical and bizarre activities; noisiness and destructive behaviour. (b) Affective disorders: hypomanic and manic states; states of agitated depression; paranoid disturbances in involutional psychoses. (c) Acute 'brain syndromes': states of intoxication, delirium and hallucinations. (d) Chronic 'brain syndromes': states of restlessness, confusional activities, violent outbursts, noisiness and destructive behaviour. (e) Psychoneurotic and personality disorders: tormenting feelings of tension, aggressive acting out and poor impulse control.

The latter category is the most problematical. The diagnosis of personality disorder, in particular, is a very controversial topic and the administration of powerful drugs, like the antipsychotics, has led to allegations that these drugs are used to quieten inmates of non-medical institutions, such as prisons and detention camps.

Treatment of acute schizophrenia

Antipsychotic drugs have long been the mainstay of treatment in acutely ill schizophrenic patients. After 30 years of intensive use, however, it is clear that antipsychotic medication does not cure schizophrenia. The condition is contained so that the acute, initial attack is cut short and subsequent relapses minimized. The effects of the acute attack on the patient and on his social functioning are ameliorated and long absences from work may be avoided. Nevertheless, some patients still pursue an inexorable course with deterioration and eventually relegation to the long-stay wards of the asylum.

The effectiveness of antipsychotic medication in the treatment of the acutely ill schizophrenic has been established in hundreds of trials, including some very carefully controlled ones involving hundreds of patients.

A large American trial, carried out under the aegis of the National Institute of Mental Health, allocated at random 463 newly admitted acutely schizophrenic patients to treatment with chlorpromazine, fluphenazine, thioridazine, or placebo. Each drug was given in flexible dosage, that for chlorpromazine averaging 655 mg/day. The psychiatrist in charge made global assessments. A total of 344 patients completed 6 weeks of treatment, most dropouts receiving placebo. Since only the less severely ill patients completed treatment, the results are actually biased against the phenothiazines. None of the drug-treated patients deteriorated, 5% did not change, 20% improved minimally, but the majority, 75%, improved substantially. Fewer than 40% of those given placebo improved substantially.

In this trial, the three phenothiazines did not differ. In another trial, however, eight phenothiazines were compared in 322 newly admitted patients with mixed diagnoses, all considered suitable for phenothiazine therapy. The overall effects of the drug administered in flexible dosage for 30 days did not differ. But three of the phenothiazines — prochlorperazine, perphenazine and fluphenazine — were more effective than the others in managing the more severely ill patients. By contrast, thioridazine, trifluopromazine and thioperpaze were more beneficial in the less ill patients. Chlorpromazine was intermediate in effects and trifluoperazine was inconsistent.
A large-scale comparison of five treatment programmes in acute schizophrenia showed drug therapy alone to be almost as effective as drug therapy plus psychotherapy and both these regimens to be more effective than psychotherapy alone, or ‘milieu’ therapy, i.e. routine ward therapy. Electroconvulsive therapy was more effective than psychotherapy but less so than drugs.

Recently, antipsychotic medication was evaluated by a group of Australasian psychiatrists as part of their treatment outlines for the management of schizophrenia. To that end, a meta-analysis was carried out of over 100 trials comparing various treatments. Meta-analysis combines the results of trials to calculate an overall ‘effect size’ in terms of the differences between end-scores of the various treatment groups, standardized statistically. Hospitalization with usual ward care was the standard basis for comparison. Psychotherapy did not prove additionally beneficial and the two studies of social intervention showed little effect. Drug therapy, however, did effect a considerable improvement which psychotherapy did not augment further. The addition of social intervention enhanced improvement but only three trials were involved.

Overall, it seems clear that the most helpful therapeutic step in managing acute schizophrenia is the administration of antipsychotic medication, thereby hastening resolution of the psychotic episode. Whether the ‘natural history’ of the condition is modified is unclear partly because of the problems of conducting such studies. Klein and Davis assessed a number of controlled studies and concluded that Bleuler’s fundamental symptoms, namely, thought disorder, blunted affect, withdrawal and autistic behaviour, were at least as much improved as other less specific symptoms, such as auditory hallucinations and paranoid ideation. This, however, does not necessarily imply that the process of schizophrenia itself is being modified, merely that the whole spectrum of symptoms is amenable to improvement.

Prevention of relapse

The term ‘maintenance therapy’ describes the long-term treatment with antipsychotic drugs of schizophrenic patients in remission. Such patients may be living in sheltered accommodation in the community, with relatives or in lodgings, or they may be inmates of a long-stay psychiatric ward. The antipsychotic drugs suppress chronic symptoms such as hallucinations, render delusions less insistent and generally help prevent the periodic episodes of more acute symptoms which punctuate the course of many schizophrenic illnesses.

Several items of patient behaviour can be used to measure response, including rehospitalization rate, adjustment at work, residual symptoms and social functioning. An analysis of over 20 controlled studies of antipsychotic medication prescribed for longer than 1 month concluded that patients taking drugs were much less likely to relapse than those maintained on placebo. For example, Pasamanick et al. reported that over 80% of schizophrenics were able to remain out of hospital for 18 months or more when maintained on drugs as compared with control patients given placebo of whom half relapsed. The results of various studies differ as to whether maintenance therapy prevents relapse or merely postpones it; the reasons for discrepancies include the different types of patients studied, the degree of social support provided and the type of medication. Postponement seems to be the usual type of effect produced: roughly, the chance of relapse is halved by drugs as compared with placebo.

During 1 year’s maintenance therapy with phenothiazines, about one-third of patients relapsed as compared with four-
fifths of those on placebo. These authors recommend that patients having a first attack, incorporating depressive features yet having a good previous personality, should not be entered routinely into a standard maintenance programme. In this study, the patient sample was taken from the middle third of the range of schizophrenic patients with respect to prognosis. Patients excluded from the trial because of their poor prognosis did badly in spite of drug treatment; those with a good prognosis did well without drugs.

In such studies a complication is that an undetermined proportion of patients who relapse either reduce their dosage or cease taking their drugs altogether. Patients may either stop taking their drugs and then relapse or spontaneous relapse may be associated with an increasing reluctance to persist with medication. Early signs of psychotic relapse were identified in a study in which antipsychotic drug withdrawal was followed by relapse in 26 of 32 schizophrenic out-patients. Important factors included positive psychopathology, motor dysfunction, impaired affect and sleep disturbance. Relapse could be prevented by starting drug therapy again when these prodromata appeared.

The value of social work in relation to continued antipsychotic medication was examined by allocating patients randomly to drug treatment, with or without counselling by a social worker, or to placebo with or without such help. The counselling was directed towards aiding the patient adjust to his or her 'major role' as wage-earner or homemaker. After 2 years, 80% of placebo-treated and 48% of drug-treated patients had relapsed. Effects attributable to social work intervention were much less than the drug-placebo differences but it did reduce relapse rates in patients who remained in the community for more than 6 months. For such patients, combining drugs with help from the social worker provided the optimum treatment. Drugs were most effective in patients with stable family backgrounds and supportive relatives, and in housewives. Social worker aid was most efficacious when the patient's symptoms had been controlled by medication.

Important insights into the role of relatives in influencing the relapse of schizophrenic patients stem from the work of Vaughn and Leff. Data were available from 128 schizophrenic patients maintained in the community, of whom 30% relapsed over 9 months. Depending on the number of critical, hostile and emotionally involved comments made about the patient during a standard interview by the relative with whom he or she lived, the patient's home environment was categorized as high or low in 'expressed emotion' (EE). In patients living in a high EE home the relapse rate was 51% as contrasted with only 13% of those in low EE homes. The number of hours the patient spent with the key relative was also a factor: patients in high EE homes who spent <35 h/week with their relatives had a much lower relapse rate (28%) than those with >35 h/week of contact (69%). Further protection was provided by regular antipsychotic maintenance therapy. In patients in high EE homes, with <35 h/week contact and taking drugs regularly, the relapse rate (15%) approximated to that in patients from low EE homes. By contrast, the relapse rate was 92% over 9 months in patients in high EE home environments, with >35 h/week contact and not taking medication. Drug therapy did not affect the prognosis in low EE patients. A 2-year follow-up showed a reverse of this differential protective effect: at that time, drugs lowered the relapse rate in low EE patients but had no effect in high EE patients. A more recent study, however, showed few positive results and the authors concluded that social factors are weak predictors of liability to relapse.

Long-acting depot injections have been shown to be a definite advance over oral
medication especially in the maintenance therapy of chronic schizophrenics in the community.\textsuperscript{39-41} One reason for the better results lies in the different mode of administration: intramuscular injection avoids the first-pass metabolism undergone by much of the orally administered drug. Another reason is the reduction in drug defaulting.\textsuperscript{42} With oral medication, perhaps as many as a half of schizophrenic patients fail to take their medication as prescribed. When non-psychiatrically trained nurses are responsible for the depot injections and many agents are involved, about one-third of patients default. When administrative supervision is simplified to one agency and trained psychiatric nurses give the injections, only one in seven patients default. Thus, as a rough guide, the default rate can be reduced by at least a half by switching from oral to depot medication. Furthermore, defaulters can be immediately identified and followed-up.

Benefits from injections have been quantified in several ways.\textsuperscript{43} In the earlier trials, patients on oral medication were switched to depot injections: marked clinical gains were apparent with between a 30\% and 70\% reduction in relapse rate. These improvements were attributed by some to non-specific factors, such as therapeutic enthusiasm and increased social support. Fully controlled double-blind trials, however, have demonstrated that the clinical benefits of the depot preparation depend on the drug content. Nevertheless, the prognosis even with depot injections leaves much room for improvement as about one-third of patients are likely to relapse over 2 years.\textsuperscript{44-46}

**Chronic hospitalized schizophrenics**

One early review of 29 investigations of the therapeutic effects of chlorpromazine in chronic schizophrenic patients established that the drug produced a statistically significant global response with particular improvement in symptoms such as anxiety, restlessness and tension.\textsuperscript{47} Positive results tended to be associated with higher dosage and longer duration of treatment, the less chronic the condition the better the therapeutic response. Patients with the highest initial ratings of tension derived the greatest benefit from antipsychotic drug treatment.

Despite this, it is generally agreed that antipsychotic drugs have less effect on the symptoms and behaviour of chronic schizophrenics than those of more acutely ill patients. Some psychiatrists have concluded that these drugs are of little value in the management of inert, withdrawn, passive patients whereas others dispute this, finding that overactive patients are also not greatly helped. Various trials show different profiles of action which all suggest that antipsychotic drugs have relatively minor effects in chronic schizophrenics in hospital. Patients with organic brain changes seem particularly unresponsive.\textsuperscript{48} The emphasis has moved towards evaluating the interactions of antipsychotic medication and other forms of therapy, particularly social and occupational rehabilitation programmes. Intensive occupational therapy produces improvements which, at least initially, equal those produced by chlorpromazine alone, but the addition of the drug enhances the non-specific effects of rehabilitation therapies.

**UNWANTED EFFECTS**

In view of the many pharmacological actions of the antipsychotic drugs, it is hardly surprising that many unwanted effects occur.\textsuperscript{49} Idiosyncratic responses are also common. The dopamine-blocking effects of antipsychotic drugs are generally held to underlie their therapeutic effects. This blockade is also deemed responsible for several different types of neurological disorders secondary to dopamine blockade in the basal ganglia.
Extrapyramidal syndromes

Acute dystonia. The earliest neurological effect during a course of antipsychotic treatment is acute dystonia. It may supervene even after a single dose of a high potency compound, such as fluphenazine or haloperidol, and it occurs in about 2.5% of patients treated with antipsychotic drugs. It is more frequent in men and children than in women. The features are diverse and often bizarre, including torticollis, retrocollis, facial grimaces and distortion, tongue protrusion, dysarthria, opisthotonos, scoliosis and oculogyric crisis. The condition may be misdiagnosed as tetanus, tetany or even hysteria but the history of taking an antipsychotic drug usually clarifies the diagnosis. Prompt relief usually follows the intravenous injection of diphenhydramine, benztropine or biperiden. Oral administration of antiparkinsonian drugs may then be needed if the condition threatens to recur. The antipsychotic medication must be discontinued or its dosage reduced.

Akathisia. Literally, akathisia means ‘unable to sit’ and it is an uncontrollable motor agitation with fidgetting, inability to sit still, constant pacing and a restless urge to keep on moving. There is a strongly subjective element with unpleasant feelings. Possible subtypes have been suggested. It occurs frequently and may be misdiagnosed as a sign of mounting psychotic agitation and treated inappropriately by raising instead of lowering the dose of antipsychotic agent. Akathisia is sometimes helped by a benzodiazepine but antiparkinsonian drugs are usually ineffective. It is commonest after 1–2 weeks of antipsychotic treatment but it can appear later.

Parkinsonism. This is the most frequent of the neurological conditions related to antipsychotic treatment. The mildest form is bradykinesis often detectable in the patient’s handwriting which becomes minuscule (‘micrographia’). Then akinesia occurs with weakness in muscles used for fine repetitive actions. In the more severe forms, there is loss of associated movements, rigidity, stooped posture, festinant gait, mask-like facies, coarse ‘pill-rolling’ tremor, excess salivation and seborrhoea. The condition occurs more frequently in women than in men and is also common in patients who have relatives with idiopathic parkinsonism. It is more common in the elderly and may be mistaken for apathy, depression or dementia. It usually supervenes after 1–2 months of treatment but can be delayed for much longer when it may remain unrecognized. Some degree of tolerance develops to this extrapyramidal effect as it tends to disappear after a few months. At modest dosage of chlorpromazine (600 mg/day), its incidence is 15–25% depending on how assiduously it is sought. With thioridazine the incidence is much lower and with piperazine-type compounds and haloperidol somewhat higher.

Uncommon reactions. These comprise akinetic mutism and catatonic reactions which may occur on high doses of the potent piperazine phenothiazines and butyrophenones. Withdrawal dyskinesias, taking the form of choreo-athetotic reactions lasting a few days, have been described when such high doses are abruptly discontinued.

Neuroleptic malignant syndrome. Another condition is neuroleptic malignant syndrome with muscular rigidity, hyperthermia and autonomic dysfunction. This condition has occasioned concern fairly recently. It was first called ‘syndrome malin’ in the French literature: reported cases have been sporadic and total less than 150 worldwide but the condition is much more widespread than that. The drugs most often implicated are haloperidol,
chlorpromazine and fluphenazine. The rate of increase of drug load seems an important factor in the aetiology. The motor symptoms comprise catatonia, akinesia, tremor, chorea and changes in muscle tone which may cause dysphagia, dysarthria and dyspnoea. The most important autonomic symptom is hyperpyrexia but many others have been reported. Management of neuroleptic malignant syndrome involves withdrawal from the antipsychotic drug and the institution of supportive measures. Specific drug measures which have been advocated include dantrolene, as a muscle relaxant, and bromocriptine, to facilitate central dopaminergic mechanisms.

There is no evidence that routine antiparkinsonian medication will prevent extrapyramidal syndromes developing but anticholinergic effects are potentiated. Particularly inadvisable is the further addition of a tricyclic antidepressant as now three anticholinergic drugs are being given. Severe somatic effects, such as urinary retention or paralytic ileus, have been described and a confusional psychosis is possible. Finally, antiparkinsonian drugs may lessen the effectiveness of antipsychotic medication by interfering with drug absorption or accelerating drug metabolism. For these reasons the rational prescriber avoids using antiparkinsonian drugs and relies instead on a careful reduction in antipsychotic drug dosage. The exception is when lowering the dose is followed by an unmanageable increase in symptoms. With the depot neuroleptics, lowering the dose or increasing the period between injections tends to reduce extrapyramidal effects. Sometimes antiparkinsonian medication is needed for a few days in each injection cycle, typically the first week. If antiparkinsonian drugs are given, they should be gradually withdrawn after a few months. Parkinsonian effects do not usually recur, although this assertion has been challenged.

Tardive dyskinesia
Tardive means belated and these dyskinesias are typically seen after several years of antipsychotic medication. Rarely, tardive dyskinesia may supervene after only a few months of treatment. The prevalence is quite high, especially in in-patients on depot antipsychotics where surveys have shown about 30% prevalence. There is about a 10-20% prevalence in those taking oral medication and about half this frequency for out-patients on oral medication. Estimates vary widely, however.

Tardive dyskinesia is characterized by co-ordinated, stereotyped involuntary movements, which fluctuate in severity, disappear during sleep and increase during emotional arousal. Severity ranges from the barely detectable to crippling and, rarely, life-threatening intensity. A number of scales exist for rating the severity of tardive dyskinesia. Orofacial muscles are most likely to be affected but any muscles can be involved. In most cases the patient tries to hide the abnormal movements and belittles their importance. Nevertheless, the dyskinesia can be very unsightly and this, at the very least, adds to the problems of rehabilitating the patient in the community. Complications include mucosal ulceration, inability to wear dentures, extrusion of food from the mouth, impaired swallowing, gait, posture and even respiration, weight loss secondary to ceaseless movement and fractures. The earliest sign of tardive dyskinesia is often a quivering of the tongue or floor of the mouth. Oral movements are most characteristic in the elderly, whereas limb involvement occurs more frequently in younger patients.

Dyskinesia can also supervene early in treatment, with dystonias or parkinsonism: the lack of clarity in the classification of neurological side-effects of antipsychotic drugs probably stems from this. In addition, dyskinesias can become manifest for the first time when medication is discon-
Many factors predispose to tardive dyskinesia. Age is important both in the incidence of the condition and its reversibility: older patients are more likely to develop an irreversible form. Females have a slightly higher incidence than males. The condition is not confined to schizophrenics and brain damage is also implicated in a complex way. Although dyskinesias can occur in elderly people who have never taken psychotropic drugs, the likelihood is several-fold in those who have used antipsychotic drugs in the past. Both dosage and duration of therapy have been implicated but no close relationship between either factor or incidence has been proved. It is unclear whether some antipsychotic drugs are more likely to induce tardive dyskinesias than others. Anticholinergic drugs accentuate tardive dyskinesia but claims that they seem to predispose to it have not been supported, nor is a challenge dose of an anticholinergic drug useful in identifying patients with covert dyskinesias.

The extent of reversibility of tardive dyskinesia after discontinuing antipsychotic drugs is disputed. In one study, only one of 33 patients with tardive dyskinesia completely lost their abnormal movements within 12 months of discontinuing antipsychotic medication: the median time to first improvement was 7 months. Partial remission of symptoms is, however, encouraging: in patients kept off medication for 18 months, the estimated probability of showing a halving of movements was nearly 90%.

The most popular hypothesis for the pharmacological mechanism underlying this syndrome is that dopaminergic systems in the basal ganglia become hypersensitive to compensate for prolonged blockade of the dopaminergic receptors by the antipsychotic medication. This may be analogous to a 'denervation supersensitivity.' Thus, the initial extrapyramidal syndrome of impaired dopaminergic transmission, namely parkinsonism, wears off as supersensitivity overcomes the block; later, as the supersensitivity increases, dopaminergic overactivity is manifested as dyskinesias. This hypothesis explains some, but not all, clinical observations and new hypotheses have been advanced. Tardive dyskinesia might reflect blockade of a subset of striatal dopamine receptors or a reduced turnover of γ-aminobutyric acid in striato-nigral pathways.

Attempts to treat tardive dyskinesia are generally unsuccessful, at least in the long run, suggesting that dopaminergic supersensitivity continues to increase. Thus, increasing the dose of antipsychotic medication or substituting a high potency compound, such as pimozide, effects only a temporary improvement. Similarly, a dopamine-depleting drug, such as tetra-benazine, is useful for only a short while, and the dysphoria and depression produced by reserpine-like drugs limit their use. Cholinergic compounds, such as the precursor choline and deanol, have been disappointing, as has lithium. γ-Aminobutyric acid potentiating drugs, including sodium valproate and the benzodiazepines, show minor effects but may act non-specifically as sedatives.

When treating a patient developing tardive dyskinesia, the clinician should carefully assess the severity of the abnormal movements and the degree of activation of the psychosis. The use of antiparkinsonian drugs should be tailed off and neuroleptic medication should be slowly reduced in dose until total discontinuation or until the symptoms of the psychosis become troublesome. Addition of a benzodiazepine may allow a little further reduction in dose.

The goal should be prevention. The use of antipsychotic drugs should be confined to definite major indications, especially in the elderly and the brain-
damaged, and the lowest possible dose should be prescribed. Patients should be examined frequently to detect early signs of tardive dyskinesia, as it is then usually reversible. As the incidence of tardive dyskinesia is higher in patients receiving depot injections, these should only be used when definite medical indications exist and not for administrative convenience. Anti-parkinsonian drugs should be avoided wherever possible, never prescribed routinely, and withdrawn after 3 months or so.

Other 'tardive' syndromes have been described and include tardive or rebound psychosis, tardive Tourette's syndrome, tardive akathisia and tardive dystonia. The distinct nature of these entities has not been established. As with tardive dyskinesia, the treatment of tardive dystonia is disappointing.

**Autonomic effects**

The powerful anticholinergic effects of thioridazine and, to a lesser extent, chlorpromazine are manifested as dry mouth, blurred vision, difficulty in urination and constipation. These effects are much less with the high potency piperazine phenothiazines and butyrophenones. Although usually merely troublesome, occasional severe effects include urinary retention, paralytic ileus and oral infection, especially if the antipsychotic drug is combined with antiparkinsonian and antidepressant therapy.

The sympatholytic actions of antipsychotic drugs are due to α-adrenergic blocking actions and comprise orthostatic hypotension with reflex tachycardia, and delayed or inhibited ejaculation.

**Endocrine and metabolic effects**

The secretion of prolactin is increased by antipsychotic medication due to dopaminergic blockade. Alterations in oestrogen and testosterone levels have also been reported. Galactorrhoea, often with amenorrhea, is commonly seen in women. Sexual disturbance with loss of libido may occur in men. Growth hormone levels are lowered but retardation of growth does not seem important in children maintained on phenothiazines or butyrophenones. Weight gain is often marked reflecting increased appetite and decreased activity.

**Psychological effects**

Many antipsychotic drugs produce excessive sedation which usually wears off fairly rapidly. A few of these drugs, mainly piperazine phenothiazines, are somewhat stimulatory. Dizziness and muzziness are usually due to postural hypotension.

The induction of depression of mood by antipsychotic medication is a complex and controversial topic. Irrespective of medication schizophrenic patients may show pronounced affective swings. Schizophrenia may present initially as a depressive syndrome and suicide is 50 times more common in schizophrenic patients than in the general population. The relationship of affective changes to antipsychotic medication is, therefore, difficult to clarify. Further, the akinesia of extrapyramidal origin can be mistaken for depressive retardation. Withdrawal effects may follow the discontinuation of low potency antipsychotic drugs, such as chlorpromazine; they include insomnia, anxiety and restlessness.

**Adverse effects**

The antipsychotic drugs are associated with a long list of adverse effects, most of which are uncommon. Indeed some of these adverse effects have become less common over time since the introduction of the phenothiazines, cholestatic jaundice being an example. This syndrome is probably allergic in type as fever, eosinophilia and rashes accompany the jaundice. The jaundice is almost always benign, remitting when the drug is stopped. Biliary cirrhosis may rarely supervene. Agranulocytosis is
also rare, occasional cases having followed the use of chlorpromazine and thioridazine; it is almost unknown with the high potency piperazine phenothiazines, thioxanthenes and butyrophenones. Clozapine is an anti-psychotic drug which has a particular propensity to induce agranulocytosis. Recent evidence, however, suggests that it is more efficacious than other antipsychotic drugs in treating drug-resistant patients so its risk—benefit ratio is still favourable in such patients.

In high dosage (>600 mg/day) thioridazine presents the risk of inducing pigmentary retinopathy and blindness. This is totally distinct from the accumulation of chlorpromazine and related compounds in cornea, lens and skin, forming purple—grey pigmentation. This adverse effect is more common in sunny climates.

The phenothiazines, especially thioridazine, induce abnormal T-waves in the electrocardiogram, perhaps by altering potassium disposition in the myocardium. Life-threatening arrhythmias are, consequently, more likely and may underlie instances of sudden death in patients on phenothiazines. 

Toxicity in overdose
Intentional overdoses with psychotropic drugs are very common, schizophrenic patients often attempting suicide by taking overdoses of antipsychotic medication. Accidental overdosage is seen in children. The toxicity of these drugs is low relative to the barbiturates and the tricyclic anti-depressants, with a low mortality rate.

The earliest signs of overdose are drowsiness with or without agitation and confusion. Dystonias, twitching and fits may be seen and the electroencephalograph contains prominent slow waves. Hypotension is often profound, cardiac arrhythmias may supervene; hypothermia is common and may be profound. Anticholinergic effects are especially marked with thioridazine and worsen the prognosis. Extrapyramidal reactions are usually not a problem, perhaps because they are counteracted by the anticholinergic actions of the drug.

REFERENCES


