Drug strategies and treatment-resistant schizophrenia

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Objectives: The aims of the paper are to review the notion of treatment resistance in schizophrenia and consider the factors important in determining non-responsiveness to standard neuroleptic treatment, and to review the strategies currently available in the treatment of such patients, including an evaluation of recently-introduced, novel drug treatments.

Method: A selective review of the literature relating to treatment resistance was undertaken using medline searches, followed by cross-checking for further articles identified in these references.

Results: The various treatment approaches available are considered, including adjunctive treatment with lithium or carbamazepine. The risks and benefits of high dose antipsychotic treatment are discussed. The possible benefits and side-effects of new treatments, particularly the atypical neuroleptics, are also reviewed.

Conclusions: The reasons why a proportion of patients with schizophrenia fail to respond to standard neuroleptic treatment are ill-understood. Nevertheless, initial assessment should include identification of any factors that may be related to a patient's poor response, such as poor compliance, substance use or epilepsy. This may help to determine an appropriate treatment strategy. There is a need to be systematic and to ensure that patients be given an adequate trial of each treatment tested in terms of duration and dosage. The available evidence does not support the use of high doses of neuroleptics for the majority of patients. Adjunctive treatments, such as lithium, carbamazepine or benzodiazepines may be beneficial in non-responsive patients, particularly if certain target symptoms are present. Atypical neuroleptics, particularly clozapine, have proved particularly effective in non-responsive patients as well as those sensitive to the motor side-effects of standard drugs. However, the high risk of agranulocytosis with clozapine is a problem; also, the drug and the necessary haematological monitoring are expensive. There are hints that some of the other, new, atypical neuroleptics have some benefit in non-responsive patients, but controlled studies are required.

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It has been suggested that as many as 25% of patients with schizophrenia show minimal response to treatment with the traditional antipsychotic drugs [1,2]. A proportion of such patients will remain in hospital for long periods with continuing psychotic symptoms and psychosocial disabilities. Such patients require the sustained efforts of highly specialised staff and mental health resources. Although the management of such patients continues to present a major challenge, the recent introduction of the novel atypical neuroleptic drugs has provided renewed enthusiasm and therapeutic optimism. These so-called atypical neuroleptics have been more readily available overseas, but some, such as clozapine, risperidone and remoxipride (subsequently withdrawn), have recently been introduced into Australia [3]. Others, including olanzapine and seroquel, are currently under investigation in controlled clinical trials. Although such innovations are important break-throughs in the management of non-responsive patients suffering with schizophrenia, it is important that the therapeutic strategies adopted for these patients are systematic and thorough. In this way the reasons for treatment failure will be evaluated adequately for individual patients. In this review, the factors governing treatment non-responsiveness will be considered and some of the newer atypical medications will be discussed.

Defining treatment resistance

There are no established guidelines for predicting response to drugs or identifying those patients likely to be resistant to drug treatment [4,5]. Similarly, there are no accepted or validated criteria for defining treatment refractoriness, which makes it difficult to interpret the findings from the limited number of adequately conducted studies investigating the effectiveness of various treatment strategies in such cases. The problem of definition is exemplified by recent suggestions by some authors of a less restrictive notion of treatment refractoriness: for example, Meltzer [6] has suggested that "schizophrenic patients who do not return to their best premorbid level of functioning – adjusted for the disruptive effect of the 'time out' from their previous activities, for the effects on self-esteem and confidence, and for the reactions of their environment that might occur with any mental illness – should be considered treatment resistant to the extent that their previous level of functioning is further impaired." While this may be helpful for patients who might otherwise be excluded by stricter definitions, to commence newer treatments it is important to separate rather than confound these issues. Meltzer's broad definition could be over inclusive and present difficulties for reliability between raters and for the comparison of results between different studies.

In their review of the data from the multicentre studies conducted by the NIMH Psychopharmacology Research Branch in the 1960s, Davis and colleagues [7] found that almost 10% of newly-admitted patients receiving treatment with antipsychotic drugs were rated as "no change" or "worse". Kane *et al* [8] concluded from these data that 10–20% of patients derived little benefit from conventional antipsychotic drug therapy, although a smaller proportion would seem to be completely resistant. For example, May [9] found that 6 out of 92 drug-treated patients (4.4%) could not be discharged from hospital within 6 months. Further, in a study of first-episode schizophrenic patients [10], 17 (6.5%) of the 253 patients in the sample did not achieve discharge within the 2 year follow-up period, predominantly owing to the persistence of positive symptoms. Follow-up data from first-episode psychosis patients discharged from the Early Psychosis Prevention and Intervention Centre (EPPIC) in Australia suggested that 10% of patients with schizophrenia spectrum had persistent psychotic symptoms for up to 12 months post-discharge [Edwards, McGorry *et al*, personal communication]. In their follow-up of 58 young patients with chronic schizophrenia, Breier and colleagues [11] found that when patients received optimal neuroleptic treatment, levels of positive and negative symptoms predicted outcome levels of symptoms, duration of hospitalisation and level of functioning.

Reasons for failure to respond

If a patient fails to respond to an adequate trial of 4–6 weeks of antipsychotic medication in conventional dosage, several possible explanations should be considered, including patient, illness and treatment factors [12] (Table 1).

Patient factors

Relevant patient variables include organic factors, such as brain structural abnormalities as may be evident on MRI, and the use of substances, such as

amphetamines, cocaine or cannabis [13,14]. Psychological factors have also been recognised, including high levels of expressed emotion. Other socio-environmental factors, such as lack of social support or stress at work or elsewhere, may also influence treatment response.

Poor compliance with drug treatment – sometimes termed "treatment reluctance" – is a serious clinical limitation on drug therapy that can prolong psychosis, cause unnecessary relapse and increase the potential for violence in the community [15,16]. Mann [17] has estimated the proportion of schizophrenic outpatients failing to comply accurately with instructions regarding prescribed medication as around 35%, although figures of up to 63% have been reported for oral antipsychotics. Even with psychiatric inpatients, 10–30% will default on their medication persistently. The poor compliance figures of 30-50% reported in some maintenance studies [18] are all the more striking if one considers that clinical trials are likely to recruit the more cooperative patients.

The major consequence of poor compliance is an increased risk of relapse: for example, in a one-year follow-up of 86 discharged schizophrenic patients, Gaebel and Pietzcker [19] found that only 28% of those patients receiving continuous medication were readmitted to hospital compared with 55% of those whose treatment was discontinued or intermittent.

A crucial factor in establishing and maintaining improved treatment compliance is the establishment of a good therapeutic relationship, which should be the aim from the outset of treatment. For example, in their study of 143 patients with schizophrenia, Frank and Gunderson [20] demonstrated that patients who formed good treatment alliances with therapists were more likely to comply with medication, had a better outcome at two years and required less medication. Importantly, the findings from this study suggested that the first 6 months was the critical time for the development of such an alliance. The development of a therapeutic alliance with the patient who has not responded to treatment will be facilitated by an appreciation of the effects of treatment from the patient' s point of view. For example, the presence of side-effects which distress the patient may be important determinants of poor compliance. As Corrigan *et al* [16] point out, there is a need for collaboration between patient and doctor when establishing patients on individualised treatment regimens.

To overcome the problem of inpatients not swallowing tablets, some oral antipsychotics are available in syrup form so that administration virtually guarantees ingestion. However, long-term use may increase the risk of dental caries and weight gain. The use of a dosette box containing a weekly or daily supply of medication, and which is filled regularly by a nurse, may help to ensure regular tablet-taking in those patients who have difficulty remembering to take their medication but who are otherwise compliant. Compliance may also be facilitated by using simple regimes (e.g. once or twice daily doses), fewer tablets and the use of "community treatment orders".

Theoretically, compliance difficulties should be partly overcome with depot preparations. One advantage for depot injections is that if a patient relapses despite regular administration, it is then clear that compliance was not an issue and other factors contributing to psychotic relapse need to be considered. However, the reduction in compliance problems by using depot medication may be less than imagined. A consistent finding in studies [21,22] has been a failure rate of around one-third for patients becoming established on depot injections after discharge from hospital. Also, there is some evidence that those patients failing to attend for their injections would also be the unreliable tablet-takers. Thus, those patients attending regularly for their depot injection are probably not those in whom defaulting with oral drugs would be a major problem.

Further, even in a population of patients who are established on depot treatment, compliance can be a serious problem and associated with relapse. In the follow-up study by Curson *et al* [23], 40% of the patients had presented some problem of compliance with their injection regime over a seven year period. There were significant correlations between the number of illness episodes and poor compliance. However, it is not possible to unravel from such data whether poor compliance is a cause or effect of clinical deterioration, or a combination thereof.

Illness factors

The negative symptoms characterising the Type II syndrome were initially described by Crow [24] as being unresponsive to drug treatment. While the consensus view at present is that negative symptoms are not appreciably aggravated by neuroleptic medication, opinion is divided as to whether or not these

Table 1. Potential factors in treatment-resistant schizophrenia

PATIENT FACTORS
Psychological (e.g. poor compliance)
Premorbid factors (e.g. early trauma, personality, behavioural disturbance, poor education and cognitive functioning)
Cultural background and expectations
Familial stress/hostility/emotional over-involvement
Lack of social support/stress at work or elsewhere
Dual diagnosis (organic, e.g. brain atrophy; substance abuse, e.g. amphetamines, cannabis; mental retardation)

ILLNESS FACTORS (related to schizophrenia)
Negative symptoms
Primary/secondary
Poor treatment response to drug treatment
Poor prognosis patients
Earlier age at onset of illness
Prominent negative symptoms during 1st illness episode
Poor response to drug therapy at an early stage
Type 1 *vs* Type 2 schizophrenia
"Neurodevelopmental" vs "adult" types of schizophrenia
Presence of cognitive impairment (e.g. frontal lobe features)
Biological toxicity of the illness

TREATMENT FACTORS
Inadequate dosage/dosage too high
Inappropriate drug treatment
Drug interactions: anticholinergics
Deficient absorption/bioavailability problems/aberrant metabolism
Delay in initiating treatment
Absence of, or inappropriate, rehabilitation programme
Situation/environment in which treatment is given

drugs can improve negative symptoms [25–27]. Acute studies of conventional neuroleptics have tended to show improvement in both positive and negative symptoms. The apparent response of negative symptoms may be a consequence of the successful treatment of positive symptoms and relief of associated depressive features [28]. Claims for a particular beneficial effect on negative symptoms have been made for some conventional antipsychotic drugs, particularly pimozide [29,30], low-dose sulpiride [31] and amisulpride [32,33].

Atypical neuroleptics such as clozapine [34], remoxipride [35] and risperidone [36] have also been shown to benefit both positive and negative symptoms, their effect on the latter being superior to that of standard neuroleptics. There are two issues raised by such findings. First, for fixed-dose, comparative studies it is not possible to calculate exact dose equivalents for an atypical and typical neuroleptic [37]. Thus, the apparent specific benefit on negative symptoms of one drug might reflect a superior effect on positive symptoms causing a reduction in secondary negative symptoms, or relatively less sedative or extrapyramidal effects: this mechanism can confound the assessment of negative features, such as flattened affect and lack of drive [28]. Carpenter and colleagues [38,39] have attempted to operationalise the deficit syndrome to overcome this difficulty.

The second problem is that atypical neuroleptics have a lower liability for side-effects. New drugs are introduced on the basis that they produce less parkinsonism or sedation, and these side-effects may partly confound negative symptom assessment. For example, Breier *et al* [40] selected patients with low scores for extrapyramidal symptoms for a 10-week study of clozapine. In view of the relatively minor effects on negative symptoms seen during the study, the authors concluded that improvement in negative symptoms with clozapine may be attributable to effects on secondary rather than primary negative symptoms. Thus, it is uncertain how far the response of negative symptoms to medication in acute studies in schizophrenia should be extrapolated to chronic negative symptoms.

In the cross-sectional study by Kolakowska and colleagues [41] of 77 patients with schizophrenia of 2–20 years duration, 20 (26%) were judged to have had a poor outcome. These patients were characterised by an earlier age at onset of illness and more prominent negative symptoms during the first episode of illness. Such patients tended to show a poor response to drug therapy even during their first psychotic episode. These findings are in accord with the more recent claims by Murray and his colleagues [42,43] regarding a reclassification of schizophrenia. They consider that schizophrenia may be divided into "neurodevelopmental" and "adult" types, the former group having a poor response to antipsychotic treatment. The "neurodevelopmental" patients are usually male, with a poor premorbid adjustment and an early age of onset of illness. Other characteristic features include cognitive impairment, negative symptoms, cerebral ventricular dilatation and medial temporal

lobe abnormalities. The "adult" type of schizophrenia, however, tends to occur in females, with a later age of onset, more affective symptoms and a good response to medication. Cognitive impairment and the presence of negative symptoms have been suggested to be of major importance in the failure of some patients to derive adequate benefit from drug treatment and other rehabilitative strategies [44].

Treatment factors

Patients may not respond to treatment with a particular drug because of an inadequate trial in terms of dosage and duration, and there have been suggestions that excessive dosage may also be implicated [45]. The latter may result in behavioural disturbance, including agitation, excitement and physical violence, which may be secondary to distressing side-effects such as akathisia [46]. Our own clinical observations in patients with treatment-resistant schizophrenia support this view, with patients becoming behaviourally disturbed in response to increased dosage of antipsychotic medication.

The bioavailability of oral antipsychotic drugs shows considerable variation and has been considered as a factor [45] in poor response: this variation may reflect differences in metabolism between responders and non-responders [47], or it may be due to enzyme induction [48]. Inactivation of drug in the gut, rapid metabolism during the first-pass through the liver or excessive protein binding reduce the amount of drug available centrally [45]. Drugs interacting with neuroleptics may reduce their antipsychotic efficacy. For example, anticholinergic drugs may interfere with absorption of antipsychotic drugs and thus lower plasma levels, although this is not proven. Also, anticholinergics may partially antagonise the therapeutic action of antipsychotic drugs via a central mechanism, independent of effects on plasma levels [49]. The introduction of carbamazepine reduces the plasma level of concomitant antipsychotic drugs by around 50% [50].

Whether delay in initiating treatment at the outset of illness contributes to treatment resistance has not yet been clarified. However, Wyatt [51] in his review and reanalysis of 22 studies concluded that early intervention with neuroleptics increased the likelihood of an improved long-term outcome. Studies from the first introduction of antipsychotic drugs in the USA in the mid-1950s reveal that a proportion of patients failed to respond. Six of the ten studies reviewed by Angrist and Schulz [52] noted that chronic patients showed "less brisk therapeutic responses than acute/recently hospitalised patients". This could reflect a loss of responsiveness to antipsychotic drugs over time, or could be interpreted as evidence that delay in starting treatment may predispose to a poorer outcome. Further support for the latter explanation comes from the findings of a prospective first-episode schizophrenia study by Crow and colleagues [53]. In this double-blind study, 120 patients were randomly allocated to receive either placebo or active antipsychotic drug. Within two years, 46% of the drug-treated group had relapsed compared with 62% of those on placebo. An important variable related to relapse was the duration of illness before starting medication. Relapse was significantly greater for patients in whom this period was longer than a year. This finding can be explained in terms of type of illness: that is, in illness with an inherently high risk of relapse, certain symptoms may lead to delay in hospital admission. Alternatively, it could mean that early drug treatment reduces the susceptibility to relapse: an explanation which, if true, has major clinical implications.

Therapeutic strategies for treatment-resistant patients

Faced with a schizophrenic patient refractory to medication, a number of practical treatment strategies are available maximally to benefit such a patient (Table 2). Unfortunately, there is only limited research evidence to provide clinical guidance on the assessment of such patients and treatment strategies. The importance of developing a consistent and systematic approach so that each new treatment can be adequately evaluated needs to be stressed. Otherwise a particular strategy cannot be discarded as unsuccessful and patients often end up on a number of different medications.

Assessment

It is often worthwhile to include within the reassessment of the patient a detailed review of response to previous treatments. This should establish whether past treatment regimes received an adequate trial, whether there was any evidence of benefit and whether poor compliance had been a problem.

Table 2. Therapeutic strategies for treatment-resistant patients

Assessment
Detailed review of response to previous treatments:
Has patient received adequate trials of the treatments?
Review causes of non-responsiveness,
e.g. compliance, continuing substance abuse
Current problem behaviours/mental state/cognitive functioning
Review of investigations

Non-drug strategies
Behavioural interventions
Vocational therapy
Family therapy
Social skills or communication training
Cognitive and other psychological approaches
Anxiety management
Strategies to alleviate auditory hallucinations:
e.g. subvocal speech, ear plugs or a personal stereo, psychotherapeutic techniques

Drug strategies
A. Increased dose of antipsychotic drug
No consistent advantage for high-dose therapy has been found
Potentially more fatal side-effects with high dose
Increasing the daily dose above 600 mg chlorpromazine equivalents a day gives diminishing returns, with little additional therapeutic benefit but an increased risk of motor side-effects; may be useful in individual patients
Use high potency drugs if high dose strategy to be tried
B. Decreasing the dose of antipsychotic drug
Therapeutic window
Reduction in toxicity
Supersensitivity psychosis
C. Change to another chemical class of antipsychotic drug
Two or three classes of antipsychotic drugs
Adequate doses for at least 4 weeks
D. Atypical antipsychotic drugs
Act more specifically on mesolimbic structures rather than nigrostriatal structures: e.g. clozapine, risperidone, fluperlapine, melperone, olanzapine, seroquel
E. Other treatments
Adjunctive use of lithium, carbamazepine, benzodiazepines
ECT

Current behavioural disturbances should be assessed, as these may be more important than symptoms as determinants of social functioning. The assessment should also include a review of the investigations to date and any omissions (such as urine drug screen, CT brain scan and EEG) should be considered.

Non-drug strategies

Although treatment resistance is usually defined in terms of a lack of response to antipsychotic medication, there may be psychological, social or other reasons for the persistence of symptoms or failure to survive outside of hospital. For example, drug administration may need to be accompanied by an appropriate behavioural or psychosocial intervention to tackle socially inappropriate or maladaptive behaviour. The literature suggests that a combination of drug and psychotherapeutic or psychosocial rehabilitation is more effective than drug rehabilitation alone [54]. Such measures include behavioural interventions, such as token economy, vocational therapy, family therapy, social skills or communication training, cognitive approaches and management of anxiety. Strategies to help patients with disturbing auditory hallucinations (such as the use of subvocal speech, ear plugs or a personal stereo) have also proved useful [55,56]. Recent approaches have tackled persistent symptoms using cognitive behavioural strategies [57,58].

Drug strategies

There are only very few well-controlled treatment trials in patients who have proved resistant to conventional antipsychotics [59]. For this reason patients are often placed on high doses of medication, tried on various non-neuroleptic drugs or given trials of ECT. The most common strategies are the administration of antipsychotics in high doses, trials of clozapine and other atypical neuroleptics, adjunctive treatment with lithium and carbamazepine, and ECT. When a particular drug treatment is being tested, an adequate trial – in terms of duration – is probably four to six weeks. If target signs and symptoms are identified when assessing response to a particular drug, this may help to inform the clinical decision as to whether it warrants continuation.

Increasing the dose of antipsychotic drug

In most of the studies comparing high dose to standard dose treatment, no statistically significant overall advantage for high-dose therapy has been

found [60–62]. Issues arising from this work include the lack of consistent operational criteria to define treatment-refractory cases and a wide variation in the amount of the "high", "very high" and "mega" doses used.

In most of the relevant double-blind studies in patients with treatment-resistant schizophrenia [63–67], improvement was found in a proportion of the "treatment-resistant" patients in the control group: that is, those who remained on standard dosage for the duration of the trial. This suggests that the decision that these patients had failed to respond was premature, and emphasises the importance of controlling for additional time on conventional doses of drug in such studies [4].

Nevertheless, while these findings suggest that high doses are not generally of benefit, they are not incompatible with the clinical observation that individual patients may occasionally show a dramatic response. However, potentially fatal side-effects such as pharyngeal and laryngeal dystonia and other hazards may be more likely to occur with high doses [60]. For the clinician contemplating a trial of high dose antipsychotic treatment, clinical guidelines are provided in recent papers by Hirsch and Barnes [60] and Thompson [62].

Decreasing the dose of antipsychotic drug

Often with patients who have proved non-responsive to antipsychotic medication, the dosage of drug is increased to very high levels and, as discussed, there is no evidence that this provides benefit and indeed may be harmful to the patient or be the cause of an apparent deterioration. It has been suggested that a therapeutic window exists, at least for some antipsychotic drugs, although the evidence for this remains unclear [45]. Some patients show benefit from dosage reduction, but it is not clear if this is due to the plasma level coming within such a therapeutic window or whether other effects, such as reduction in toxicity, are important [68–70]. In a clinical study to investigate this issue, Van Putten and colleagues [68] assigned acute admissions to either 5 mg, l0 mg or 20 mg of haloperidol for four weeks. From the findings, these investigators concluded that for a proportion of newly admitted, severely psychotic patients, daily doses as low as 5 mg a day of haloperidol or its equivalent may be adequate, particularly after a week or two of doses of 10 mg to 20 mg. The higher initial dose may have been helpful in sedating excited behaviour.

Baldessarini *et al* [71] reviewed 33 studies from 1959–1985 involving random assignment of 2,346 chronically psychotic patients to at least two doses of an antipsychotic. They found a consistently higher risk of motor side-effects at higher daily doses than with lower doses. Indeed, the appearance of parkinsonism and the other so-called extrapyramidal effects seem to coincide with the upper limit of the therapeutic dose range in many cases. More recently, Rifkin and colleagues [69] conducted a double blind study in 87 patients with acute schizophrenia. There were no differences in outcome between patients randomly assigned to three dosage levels of haloperidol (10, 30 and 80 mg) for a period of six weeks. They concluded that high dosages had no additional benefit. These findings are in line with reviews of the relevant literature [71] which conclude that increasing the daily dose above 600 mg chlorpromazine equivalent a day gives diminishing returns, with little additional therapeutic benefit but an increased risk of motor side-effects. According to such a review, the doses of antipsychotics currently prescribed tend to be excessive and reduction of dose may be a worthwhile manoeuvre in patients responding poorly.

Occasionally patients who are withdrawn from high doses of medication demonstrate an early acute exacerbation of illness. It has been suggested that this may be the result of a supersensitivity psychosis [72] consequent upon up-regulation of dopamine receptors in the meso-limbic system. Such a possibility would argue for gradual dosage reduction and for using the minimal effective doses of neuroleptic medication wherever possible.

Change to another chemical class of antipsychotic drug

Adequate therapeutic trials of all antipsychotic drug classes may be warranted, including the use of atypical neuroleptics. Two or three classes of antipsychotic drugs given in adequate doses of at least 400–600 mg equivalent of chlorpromazine a day for four weeks should be given before alternative approaches are tried. Although there is a relative absence of research work to inform clinical practice, a similar strategy was adopted in a study comparing clozapine – an atypical neuroleptic drug – and chlorpromazine in the treatment of patients with resistant

schizophrenia [8]. In the future, it may be possible to base treatment strategies on the profile of activity on various neurotransmitter systems by different antipsychotics, as this may determine differences in response. Thus, drugs acting to block both serotonergic and dopaminergic receptors may be more effective than specific dopamine blocking drugs. Alternatively, the effects at α2-adrenoceptors or on the various different subtypes of receptors (such as dopamine D_1, D_3 or D_4) may explain drug efficacy. Indeed, such mechanisms have been proposed as explanations for the effectiveness of atypical neuroleptics, including clozapine [73,74]. Some investigators have attempted to manipulate these neurotransmitter systems using relatively selective agents. For example, there are preliminary findings in negative symptoms for ritanserin, a selective 5-HT_{2a} and 5-HT_{2c} antagonist [75], and idazoxan, a noradrenergic α2 antagonist [76], tested as adjuncts to standard neuroleptic treatment.

Atypical antipsychotic drugs

The atypical neuroleptic drugs act more specifically on mesolimbic structures rather than nigrostriatal structures. Thus, the dose of an atypical neuroleptic necessary for antipsychotic action is generally lower than the dose which will induce extrapyramidal symptoms [77].

The atypical neuroleptics include clozapine, remoxipride, risperidone, fluperlapine, melperone (a butyrophenone), and more recent drugs, such as seroquel and olanzapine. They are characterised by minimal prolactin elevation, low incidence of extrapyramidal symptoms and an ability to diminish dopaminergic activity in the limbic system, possibly reflecting antagonism at different dopamine receptor sites [73,78].

Dibenzodiazepines

These include clozapine and fluperlapine. Fluperlapine was withdrawn because of hepatotoxicity and a high incidence of *grand mal* seizures [79].

Clozapine

This drug has been introduced recently to Australia with dramatic results in some patients [80]. From the first group of over 200 patients commencing clozapine in Australia, a survey of 83 patients revealed that 37% had substantially improved while a further 36% derived some benefit, 25% showed no improvement and 3% deteriorated [3]. The number of patients reached over 2,000 within two years of its introduction.

Clozapine is a dibenzodiazepine. It has a broad spectrum of pharmacological activity, being an antagonist at D_1 and D_2 dopamine receptors, α_1 and α_2 adrenergic receptors, and serotonergic (5-HT_2), histaminergic (H_1) and cholinergic (muscarinic) receptors [73,81]. It is one of the so-called "atypical" neuroleptics in that some clinical and pharmacological features differ from those of the classical antipsychotics: for example, it exhibits preferential blockade of D_1 relative to D_2 receptors and causes only a transient elevation of plasma prolactin. Positron emission tomography has confirmed that clozapine has a low affinity for the dopamine D_2 receptor but high affinity for the D_1 receptor in comparison with typical neuroleptic drugs [82]. Recent evidence also suggests that the novel dopamine D_3 receptor [83] and D_4 receptor [84] may be important sites of action for antipsychotic drugs such as clozapine [73,78]. For instance, some authors have speculated that the lack of extrapyramidal side-effects of clozapine and other atypical neuroleptics may be due to their action on the D_3 receptor [78] which has been localised to brain limbic areas [83]. Also, Van Tol and colleagues [84] have found that the D_4 receptor has a higher affinity for clozapine than do the other dopamine receptors. Further work is necessary to explore the relative importance of these receptor subtypes, and may lead to the development of new therapeutic compounds.

Absorption of clozapine after oral administration is virtually complete, and unaffected by food. There is extensive first-pass metabolism in the liver, and a plasma elimination half-life of 16–23 hours. Steady state is reached in 6–10 days. Excretion is mainly via the urine.

Treatment studies in schizophrenia have found clozapine to be superior to placebo and at least as effective as other antipsychotic drugs [59,78,85–87]. However, the main indication for clozapine is treatment-resistant schizophrenia [88]: this conclusion is principally based on the findings of a double-blind, multi-centre comparison of clozapine and chlorpromazine [8]. In a sample of 268 patients with schizophrenia who had failed to respond to at least three antipsychotic drugs and a prospective single-blind

trial of haloperidol, clozapine produced greater improvement in both positive and negative symptoms. Using prospective, clinically-relevant criteria of improvement, 30% of clozapine-treated patients were responders after six weeks compared with 4% of those receiving chlorpromazine. Other double-blind studies in patients with treatment-resistant schizophrenia have consistently found benefit from clozapine compared with chlorpromazine (reviewed by Mortimer [85]). The follow-up and long-term studies with clozapine suggest that there is sustained long-term benefit for the treatment-resistant patients [89]. Kane [90] concluded that clozapine is appropriate for those individuals with a serious psychotic illness who have not responded to or cannot tolerate standard antipsychotic agents. Some authors also report that clozapine is beneficial in patients suffering with treatment non-responsive affective disorders with psychotic features [91,92]. Other indications include psychosis associated with basal ganglia disorders, such as psychosis associated with Parkinson's disease [93] and Diffuse Lewy Body Disease [Nagel, Velakoulis and Pantelis, personal communication; 94].

Unwanted effects

The most serious side effects of clozapine are agranulocytopenia and agranulocytosis. These were first noted in 1975 when eight Finnish patients treated with the drug died from the complications of secondary infection [95]. The drug is associated with a high incidence of agranulocytosis of up to 2% with exposure to the drug over one year [8,96], compared with figures of 0.1 and 1.0 per thousand for conventional antipsychotic drugs [97]. More recent data for clozapine suggest a lower rate of about 1% [98]. The greatest risk for agranulocytopenia and agranulocytosis occurs between 4 to 18 weeks after commencement of treatment [96]. Possible aetiological mechanisms to explain clozapine-induced agranulocytosis include immune-mediated or toxic depression of the bone marrow [99]. It has been suggested that there may be a genetically-determined, selective vulnerability to this side-effect [89] which has been supported by the finding of an association with increased HLA antigens [100]. Other risk factors include increased age and being female [98].

Only patients with normal white blood cell counts and differential counts should be treated. Monitoring of the white blood cell count (WBC) should be carried out weekly for the first 18 weeks and subsequently every four weeks for as long as the patient continues to receive the drug. Clozapine should be withdrawn immediately if the WBC falls below 3000/mm^3 and/or the absolute neutrophil count falls below 1500/mm^3. After the drug has been stopped the WBC should be monitored weekly for one month. Treatment with granulocyte macrophage colony stimulating factor should be considered in severe cases [101]. To ensure compliance with these procedures and early warning of falling WBC, psychiatrists and pharmacists must be registered with the Clozaril Patient Monitoring Service (CPMS). The drug is only prescribed and dispensed if blood results are satisfactory. Experience in the United States indicates that this system has reduced the mortality of patients on clozapine to 1 in 6,000 [102].

The most common adverse effects seen with clozapine include drowsiness, hypersalivation, dizziness, constipation, urinary incontinence, tachycardia, nausea and vomiting, weight gain, transient hyperthermia, and hypotension. Seizures occur as a dose-related phenomenon with estimated incidence figures of around 1.4% for doses of 300–600 mg per day and 14% for doses of 600–900 mg per day [87]. If doses of 500 mg or more of clozapine are necessary, the concomitant use of an anticonvulsant such as sodium valproate should be considered [86]. This combination appears to be safe [103] and valproate causes only minor increase in the serum concentration of clozapine [104]. However, we would recommend the use of sodium valproate only when seizures are apparent, as a substantial proportion of patients will not develop seizures. Hypersalivation can be particularly distressing for patients and is often difficult to treat. The mechanism for hypersalivation is unknown, however, amitriptyline seems to be an effective treatment strategy [105] although clonidine has also proved effective [106]. Urinary incontinence has been described in a significant minority of patients, and usually occurs within the first three months of treatment [107]. Its mechanism is ill-understood and treatments include tricyclic antidepressants, anticholinergics or desmopressin [108]. Clozapine has a low liability for movement disorders such as parkinsonism and akathisia, compared with conventional antipsychotic drugs, and dystonia is rarely reported [109]. Obsessive compulsive symptoms have been reported in patients on clozapine [110].

Clozapine and tardive dyskinesia

There are no published reports of tardive dyskinesia developing with clozapine as monotherapy. The response of established tardive dyskinesia to clozapine is variable, but reports suggest that around 40% of cases – particularly those with dystonic features – will improve [111]. Casey and Keepers [112] concluded that, thus far, the drug has a very low incidence of parkinsonism or other extrapyramidal reactions. Marder and Van Putten [88] concur that there are no convincing reports of tardive dyskinesia associated with clozapine, but point out that this potential advantage of clozapine remains tentative in the absence of adequate incidence data.

Explanations put forward for the apparent lack of tardive dyskinesia with clozapine refer to pharmacological differences from the typical or standard antipsychotics. The drug causes a preferential blockade of D_1 dopamine receptors rather than D_2 receptors, and leads to an increase rather than decrease in GABA turnover. Also, as in the case of sulpiride, investigation on animals suggests that clozapine does not induce dopamine receptor supersensitivity in the extrapyramidal system [113], however, selective supersensitivity in the amygdala may occur [114]. This may be relevant to reports of rebound psychosis in patients stopping clozapine [115]: a phenomenon described as supersensitivity psychosis [72].

There is evidence for the potentiation of alcohol and other CNS depressants, MAO inhibitors and antihypertensive agents. Clozapine is contraindicated in patients with a history of drug-induced neutropenia or agranulocytosis. Patients who develop agranulocytosis on clozapine should not be re-exposed to the drug [89]. Clozapine should not be prescribed concurrently with other drugs with a potential risk of bone marrow suppression, such as carbamazepine, chloramphenicol, certain diuretics, sulphonamides, co-trimoxazole, certain analgesics and cytotoxic agents.

Clozapine offers a worthwhile alternative for patients with schizophrenia that has proved resistant to other antipsychotic drugs. In such patients, clinically significant improvement can occur early in a therapeutic trial, although improvement may be delayed by up to one year [116]. The main disadvantage of clozapine is the increased risk of agranulocytosis: a careful consideration of the potential risks and benefits, including the implications of substantial improvement in patients who have been seriously disabled with a psychotic illness for a prolonged period, is required before starting treatment.

Substituted benzamides

These include remoxipride, sulpiride, amisulpride, emonapride, sultopride, metaclopramide and raclopride. It is thought that these drugs act as selective D_2 receptor antagonists, however, recent evidence implicates the D_3 receptor [78]. Sulpiride is available in the UK. It is described in detail by Gerlach [117]. It may be of benefit in the treatment of negative symptoms of schizophrenia [31], whilst its role in patients with resistant positive symptoms has not been demonstrated. Remoxipride was available in Australia but was recently withdrawn, as discussed below.

Remoxipride

This novel substituted benzamide acts on the dopamine D_2 receptor but also has a potent action on the sigma binding site [118]. It has proved as effective as haloperidol in a double-blind multicentre study, with a suggestion of greater benefit for negative rather than positive symptoms in comparison with haloperidol [35]. Similarly, in an Australian double-blind multicentre trial remoxipride was found to be as effective as thioridazine and with fewer reported side-effects [119]. Significantly fewer extrapyramidal side-effects have been reported in controlled clinical studies [35,81]. The atypical nature of this drug may result from its selective action at subtypes of the D_2 receptor [81]. Although remoxipride is as effective as the typical antipsychotics, but with reduced extrapyramidal symptoms, its introduction has been marred by recent reports of fatal aplastic anaemia and thrombocytopaenia. It has therefore been withdrawn and its prescription has been restricted for this reason. It should be noted that clozapine was withdrawn under similar circumstances but has been reintroduced as a particularly effective drug in refractory patients. The atypical features of remoxipride may also prove useful in the management of such treatment-resistant patients, although the available evidence is not compelling [120,121].

Risperidone

This drug has been recently introduced in Australia. Although it had been considered an atypi-

cal antipsychotic, clinically it has been found to induce dystonia and akathisia. However, at its optimum therapeutic dose, it has a lower liability for parkinsonism and akathisia in comparison with haloperidol. Risperidone has a high affinity for 5-HT_2, α-adrenergic, D_2 and histaminergic sites [122]. Clinical trials have suggested that risperidone demonstrates a bellshaped response curve, with maximal antipsychotic effect at 6–10 mg [81].

Other novel drugs

Carpipramine, clocapramine and zotepine (a dibenzothiepine) have been used in Japan and are thought to have greater efficacy in patients with pronounced negative symptoms [79]. Zetidoline, a selective D_2 blocker, has been shown to be as effective as haloperidol for the treatment of positive symptoms, but with fewer extrapyramidal symptoms [123]. The pyrroloisoquinolines have been designed by computer to conform to a 3-D model of the dopamine receptor. One such compound, piquindone, antagonises the D_2 receptor, and has potent antipsychotic effects with low liability for extrapyramidal side-effects including tardive dyskinesia [77].

Drugs acting on dopamine D_1 receptors, dopamine autoreceptors as well as partial dopamine agonists are under investigation and will provide further insights about the importance and interactions of the various dopamine receptors in schizophrenia [73]. Drugs acting on other neurotransmitter systems such as 5-HT, glutamate and sigma receptors may also be of importance and are reviewed elsewhere [78,79].

Additional adjunctive or alternative drug treatments

A variety of treatments such as concurrent lithium, carbamazepine, propranolol, high-dose benzodiazepines, ECT and antidepressants have been tested in schizophrenia. So far, there are only limited data available to judge the value of such interventions, although they may be useful in patients resistant to treatment with conventional drugs. For example, there is presently little evidence for the efficacy of propranolol in patients with resistant schizophrenia; however, in his review Berlant [124] suggests some evidence for its use as an adjunct to neuroleptic therapy. Other treatments, such as reserpine and L-dopa, have been reviewed by Christison *et al* [59]. Buspirone which has been effective as an anxiolytic has also been used in schizophrenia with variable effects [125].

Lithium

Since the introduction of lithium there have been reports of its efficacy in some patients with schizophrenia, particularly those with noisy, restless or disturbed behaviour [126]. Also there have been consistent reports that poor prognosis patients and those who have shown little response to conventional neuroleptic treatment can benefit from the addition of lithium [59]. Delva and Letemendia [127] and Schulz *et al* [128] have reviewed the studies of lithium in the treatment of schizophrenia and more recently Christison and colleagues [59] reviewed the trials relevant to patients with resistant symptoms.

In their review of the double-blind studies Christison *et al* [59] conclude that lithium alone is inferior to antipsychotics as a first-line drug but may be a useful adjunct. Three double-blind studies investigated the use of lithium in patients with treatment resistant schizophrenia [129–131]. These studies used strict diagnostic criteria and a placebo-controlled, multiple crossover design. All found significant benefit from the addition of lithium as an adjunctive treatment. There was improvement in a number of areas, including psychotic symptoms, cooperation, social competence, neatness, irritability and excitement, and such improvement did not depend on the presence of affective symptoms.

In a more recent double-blind study, Lerner *et al* [132] found that schizophrenic patients with higher BPRS depression scores were the most resistant to haloperidol alone and benefited most from the addition of lithium. However, although the presence of affective symptoms may be predictive of a greater likelihood of a response to lithium in schizophrenia it is not only affective symptoms that respond [127]. Lithium may also reduce the relapse rate [133]. Some studies [131,134] suggest that the optimum response may be achieved with levels approaching the upper limit of the therapeutic range (0.9 to 1.2 mEq/l) and at least four weeks may be necessary for an adequate trial [59].

Lithium should be prescribed judiciously when used in combination with antipsychotic medication as irreversible neurotoxicity has been described [135] and reversible delirium may also occur, partic-

ularly with high neuroleptic doses [136]. Nevertheless, lithium should be considered, usually adjunctively with neuroleptics, for those patients deemed treatment failures.

Carbamazepine

This drug has proved useful in the treatment of patients with affective disorders [137] and has been used in a number of other psychiatric disorders, such as in patients with schizophrenia and more recently for the management of withdrawal from benzodiazepines [138,139]. Case reports and early uncontrolled clinical trials suggested that carbamazepine was effective in those schizophrenic patients with EEG abnormalities and aggressive outbursts or violent behaviour [140–143]. Rankel and Rankel [144] report rapid improvement in patients with catatonia.

There have been a number of double-blind studies of carbamazepine in patients with schizophrenia, a few single-blind studies and a number of uncontrolled studies [59]. Some of these have been in patients with abnormal EEG results [140,145– 147], while only a few studies investigated the use of carbamazepine in patients with treatment-resistant psychotic illness [145,148–150]. Most of these studies used carbamazepine as adjunctive treatment with an antipsychotic, while only three controlled studies have evaluated the use of carbamazepine alone in schizophrenia [149,151,152].

In his review of the relevant literature Neppe [143] concluded that carbamazepine is useful in schizophrenic patients with features such as aggression, agitation, instability and interpersonal difficulties, and who are refractory to antipsychotics alone, but that the drug is not effective with classical psychosis. This is supported by the recent well designed study by Carpenter *el al* [152], who evaluated carbamazepine against placebo in a double-blind crossover trial in 31 stabilised chronic schizophrenic outpatients. Almost all of the patients in both groups relapsed during the first phase of the study, with significant worsening of symptoms as measured by the BPRS. There were no significant differences between patients on carbamazepine and those on placebo. This study suggests that carbamazepine is not useful as a sole agent in the management of stable patients with schizophrenia.

In most of these studies the dose of carbamazepine was within the therapeutic range considered adequate for anticonvulsant action. Anecdotal evidence has suggested that patients may benefit from a high dose strategy, by attempting to achieve the maximum tolerable dose [138]. However, side-effects and interactions may limit the use of carbamazepine. Recent case reports suggest that haloperidol and carbamazepine together may cause disorientation and ataxia [153,154]. Interactions with lithium have also been described [155]. The incidence of a rash with carbamazepine, which is normally about 2–6%, may be up to 16% in psychiatric patients and this may be because these patients have received other psychotropic drugs [138,156]. Another important consideration is that the addition of carbamazepine leads to a significant decrease in plasma levels of antipsychotic drugs. Haloperidol levels are reduced by approximately 50% when carbamazepine is introduced [50,157].

The mechanism of action of carbamazepine is unclear [138]. It has a number of actions on neurotransmitter systems, including an effect on adenosine receptors. It also affects catecholamine and serotonergic systems, decreases dopamine turnover and affects neuronal cell membranes by stabilising sodium channels [158]. The action of carbamazepine as an anti-kindling agent may be relevant to its action in psychosis [159].

The available evidence suggests that carbamazepine is useful as an adjunctive treatment with antipsychotics in schizophrenia [145,150,160,161]. In particular, patients with psychosis resistant to treatment, with target symptoms such as excitement, impulsivity and aggression, and the presence of EEG abnormalities may be more likely to show a response [59]. It is probably not worthwhile as a routine treatment for patients with treatment-resistant schizophrenia.

Benzodiazepines

The results of double-blind, placebo-controlled investigations of the efficacy of benzodiazepines in patients with chronic schizophrenia suggest that the addition of a benzodiazepine can be beneficial in a proportion of such patients, with improvement usually occurring within the first two to three weeks [49]. Improvement has been reported in patients with severe anxiety, positive psychotic symptoms, tension, hostility and excitement [162–166].

Negative symptoms may also respond [163,165,167], while Altamura *et al* [168] noted improvements in parkinsonism and akathisia.

The available double-blind studies of adjunctive benzodiazepines in treatment refractory patients have reported significant benefit compared with placebo [162,165,169,170], although in two such studies no superiority over placebo was found [171,172].

While these studies suggest undoubted benefit in a proportion of patients, they also reveal a marked inter-individual variability in response to an adjunctive benzodiazepine. Generally, any positive effects reported have been modest, transient or specific for certain symptoms [173]. For clinicians considering such treatment, there are no data relevant to long-term efficacy, no guidelines for dosage and no clear indications for the use of different benzodiazepines. The potential hazards of prescribing benzodiazepines in treatment-resistant cases include disinhibition with aggressive behaviour, the risk of dependency and a rebound worsening of symptoms on drug withdrawal [173,174].

ECT in treatment-refractory schizophrenia

The literature on the use of ECT suggests that this treatment can be of benefit to patients with schizophrenia, particularly those with catatonic and affective features. However, with regard to the management of resistant schizophrenia, the literature is less clear. Salzman [175] considers that such patients derive little benefit from ECT treatment, while Meltzer [176] points out that up to 10% of such patients may respond. Meltzer [176] considers that ECT should be used only as a last resort, after pharmacological treatments have been successfully evaluated in individual patients. Such a strategy is certainly appropriate, particularly in those treatment-resistant patients who have failed to respond to the various strategies already outlined above. However, the question remains as to whether the use of ECT might be particularly advantageous in such patients at an earlier stage of treatment. Fink [177] makes the point that the combined use of ECT and clozapine should be considered earlier rather than later, particularly as the full benefits from clozapine may be delayed by up to one year [116]. Although not explicit, Fink [177] is suggesting that the therapeutic effects of drugs whose action is delayed may be hastened by the addition of ECT. This question has not been addressed in the research literature.

There have been only a few studies which have examined the effectiveness of ECT in treatment of non-responsive patients with schizophrenia [176,178–184]. Most of these studies, which are single case reports or studies of small groups of patients, would indicate that the adjunctive use of ECT with antipsychotic medication is beneficial to a significant proportion of patients [176,178,179,181–184]. In a large retrospective study, Milstein and colleagues [180] reported improvement in 60 (54.6%) of 110 treatment-resistant patients. However, these studies are not adequate to provide enough information about the characteristics of the responders, although the presence of affective features have been considered important [176]. Also, the kind of ECT which is most beneficial (unilateral *vs* bilateral, length of course, use of maintenance ECT) has not been evaluated.

The available evidence would suggest, therefore, that ECT may be an appropriate strategy in treatment-resistant schizophrenia, when other strategies have failed. However, consideration might also be given to its use as an adjunctive treatment to the strategies already described when affective features are present, or perhaps when there is a wish to shorten the sometimes prolonged time course of therapeutic action of drugs such as clozapine.

Conclusion

Standard antipsychotic medication consistently fails to produce a satisfactory response in a significant proportion of patients with schizophrenia. The recent introduction of atypical neuroleptics has stimulated therapeutic optimism for such patients. This review has mentioned possible factors contributing to treatment resistance and reviewed some of the more common treatment strategies, focusing particularly on drug therapies, including the newer medications. The new drug strategies should provide fresh hope for the psychosocial rehabilitation of the most intractable patients with schizophrenia, helping to maximise the benefits derived from other treatment strategies available. The need to adopt a systematic strategy in the pharmacotherapy of treatment-resistant schizophrenia may be decisive for successful treatment of these patients. This should be combined with a multidisciplinary approach to deal with the multi-faceted nature of the impairments encountered, including behavioural, social and communication difficulties, and cognitive deficits.

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