
Pharmacological treatment of the newly diagnosed patient with schizophrenia

Michael J. Travis & Robert W. Kerwin

The early treatment of newly diagnosed schizophrenia has ramifications for the future psychiatric and social well-being of the patient. Changes in care structures and care delivery mechanisms, in addition to financial constraints and outcome targets, provide an additional incentive to ensuring that any intervention is both successful and cost-effective.

Although it has long been acknowledged that the mainstay of treatment in schizophrenia is pharmacological, and involves the use of antipsychotic neuroleptic medication, there have been few attempts to devise a treatment protocol for first-onset patients that can be evaluated as part of a randomised controlled trial. Nevertheless, there is some evidence to guide prescribing practice.

Acute treatment of the newly diagnosed patient with schizophrenia will vary considerably according to the patient's clinical state and the need to prevent harm to self or others. Medium-term treatment should involve optimisation of therapy to the minimum effective dose and frequency. This phase of treatment should also entail a rigorous assessment of treatment resistance. This would enable patients who would benefit from clozapine to receive it early in the course of their illness. Long-term maintenance treatment of first-onset schizophrenia is a more vexing issue and involves a careful clinical risk-benefit analysis. As over two-thirds of first-onset patients will suffer a subsequent relapse without further treatment, it is an area with vast scope for minimising the morbidity associated with schizophrenia.

Importance of the first presentation

There is increasing evidence that the nature and character of an individual's schizophrenic process is established in the first few years of illness. Neuropsychological function appears to be affected in schizophrenic populations, compared with healthy controls, at illness onset, but few studies have shown any deterioration in the patients' cognitive ability over time (Goldberg *et al*, 1993). This is in accordance with the vast majority of neuroimaging studies, which consistently report little effect of illness duration on the extent of morphological brain changes.

The first two years of illness may be crucial to long-term outcome. Two studies have reported findings in accordance with previous suggestions that deterioration plateaus early in schizophrenia. Thara *et al* (1994) reported on 90 patients prospectively followed-up for 10 years. The quarter of their sample who remained affected by positive and negative symptoms had stabilised by the second year, with no evidence of further deterioration. In accordance with this, 'course type' over the two years after onset is strongly associated with course over the subsequent 10 years. (Harrison *et al*, 1996).

It is tempting to think that with early, appropriately aggressive treatment some amelioration of the long-term effects of schizophrenia may be achieved. There is some evidence that early treatment does have significant effects on outcome.

Michael J. Travis is a Clinical Research Worker in the Section of Clinical Neuropharmacology at the Institute of Psychiatry (De Crespigny Park, Denmark Hill, London SE5 8AF) and Honorary Senior Registrar at the National Psychosis Unit at the Bethlem Royal Hospital. He is involved in research into the role of neuroreceptors in the actions of antipsychotic drugs in schizophrenia. Robert W. Kerwin is Head of the Section of Clinical Neuropharmacology and the Institute of Psychiatry. He has researched and published widely within the field of pharmacology of schizophrenia and recently received the Joel Elkes International Award from the American College of Neuropsychopharmacology for outstanding contributions in this area.

Importance of early treatment

There have been two excellent recent reviews of the rationale behind the early identification and treatment of schizophrenia (McGlashan & Johannessen, 1996; Birchwood *et al*, 1997). The evidence that a longer duration of illness prior to treatment is detrimental to various measures of treatment outcome is based on a number of retrospective analyses and three prospective studies (see Box 1).

Outcome before and after introduction of neuroleptics

Wyatt (1991) reviewed a series of 19 studies, of primarily first-onset patients, which compared the outcome of those treated before beginning chlorpromazine with those treated subsequently. He noted that the use of medication increased the chances for a better long-term course. This conclusion was reinforced by Opjordsmoen (1991), who compared first-admission delusional cases ($n=151$), half of whom were admitted prior to neuroleptic treatment and half afterwards. Despite the fact that all of Opjordsmoen's cohort received neuroleptics at some point in the course of their illness, the author described significantly worse outcome for the patients who did not receive neuroleptics as their first treatment.

Retrospective studies

In a review of 10 studies relating to the first wave of patients treated with neuroleptics, Angrist & Schulz (1990) reported that in six out of 10 the response to pharmacotherapy correlated negatively with duration of illness. Results supporting these findings have been noted in studies from China (Lo & Lo, 1977), Japan (Inoue *et al*, 1986) and Iceland (Helgason, 1990). The latter study split a group of 107 on the basis of illness duration of greater than or less than one year pre-treatment. Over 18 years of follow-up, the group with pre-treatment illness duration greater than one year had a higher re-admission rate. In a smaller but significant study of 20 patients over three years, it was demonstrated that the ongoing treatment for patients with illness duration greater than six months pre-treatment cost twice as much as ongoing treatment for those who received treatment within six months of the onset of symptoms (Moscarelli *et al*, 1991).

Box 1. Importance of early treatment

Neuropsychological and neuropathological changes are evident early in the course of schizophrenia and change little with time

First two years from symptom onset characterise the subsequent course of illness

In retrospective studies of first-onset patients a longer duration of illness prior to pharmacotherapy is associated with poorer outcome

In prospective studies of first-onset patients longer duration of prodrome and pre-treatment psychotic symptoms predict a lower level of remission, and longer duration of pre-treatment psychotic symptoms are associated with a longer time to remission

Prospective studies

Three major prospective studies focusing on the duration of pre-treatment illness have all found an association between longer duration of illness and poorer outcome.

In the smaller study reporting this association, Rabiner *et al* (1986) investigated a sample of 36 first-episode psychotic patients over one year, and reported a correlation between relapse or poor outcome and longer duration of pre-treatment illness in the group with schizophrenia. In a larger study, Johnstone *et al* (1986) reported on a sample of 253 first-onset patients with schizophrenia followed-up for two years. In that sample patients with a longer duration of illness had a higher frequency of relapse. That this effect appears to continue whether patients were included in the placebo or active treatment wing of a controlled trial emphasises the importance of early treatment (Crow *et al*, 1986).

In a widely quoted two-year follow-up study, Loebel *et al* (1992) carefully and intensively investigated 70 first-episode patients diagnosed with either schizophrenia or schizoaffective disorder (mainly schizophrenia) who were included in an antipsychotic treatment protocol. They separated duration of illness prior to treatment into two components; the first included

the duration of the prodrome plus the duration of psychotic symptoms, and the second duration of psychotic symptoms alone. They reported that a lower level of remission was associated with a longer duration of both psychotic symptoms and prodrome prior to treatment. The longer the duration of pre-treatment psychotic symptoms, the longer the time to remission. Importantly, time to remission was not related to other factors, although a lower level of remission was associated with poorer premorbid functioning and an earlier age at onset. This finding of an association between better treatment response and shorter duration of pre-treatment psychosis has been replicated by Szymanski *et al* (1996).

Treatment

Treatment of the newly diagnosed patient involves a three-pronged approach using all of the skills of the multi-disciplinary team. Social and occupational therapy are an important part of helping the patient to re-establish their lives after an episode of psychosis. Psychological therapies, including family work and cognitive-behavioural therapy (CBT), are becoming increasingly well validated and may be a useful adjunct to medication, (Kuipers, 1996). However, the cornerstone of schizophrenia treatment is pharmacological (Kane & Marder, 1993), which will be the focus of this article.

Pharmacotherapy for schizophrenia can best be considered in terms of acute, medium-term and long-term maintenance treatment. No consensus yet exists in any of these three areas with regard to type or dose of drug and duration of treatment. Nevertheless, significant research contributions have been made. The re-introduction of clozapine in 1990 and the advent of several new antipsychotics over the past four years have renewed interest and optimism in the treatment of schizophrenia.

General principles

The ideal situation, for both patient and clinician, is for the patient to be receiving medication at the minimum effective dose, with a minimum of side-effects, and to be compliant with this medication. If these criteria are met, then the cost for the care of the patient is minimised, both in terms of in-patient stays and community care. It is perhaps a function of the heterogeneity of schizophrenia and the vagaries of political and health care systems that relatively little prospective research has been directed towards these issues.

Acute treatment

The acute phase is best thought of as the period between the commencement of treatment and the onset of antipsychotic effect, usually 7–14 days. Good clinical practice is to start a patient on one type of antipsychotic medication and maintain it so that they may have an adequate trial of treatment. The drug used may be crucial as it will often be the patient's first experience with medication likely to have serious side-effects and which they may have to take for many years. The choice of medication regime will depend on the patient's clinical presentation, likely compliance and the need for sedation.

The first presentation of schizophrenia is variable. The most clinically challenging presentation is that of the potentially violent or self-harming patient with florid positive symptoms. Sedation is often required, but in order to produce sedation with typical antipsychotics relatively high doses may need to be used. This increases the risk of akathisia and acute dystonic reactions (Malhotra *et al*, 1993). This is problematic as akathisia may paradoxically make the patient more agitated, and acute dystonic reactions and parkinsonian side-effects may have disastrous consequences for future compliance (Frances & Weiden, 1987).

Often in the past such patients have received high doses of sedative antipsychotics from the outset, with a reluctance to reduce doses once recovery has occurred (Thompson, 1994). However, lower doses of a typical antipsychotic, such as haloperidol 5–15 mg/day, are as effective against psychotic symptoms as higher doses while being associated with a reduced risk of side-effects (Kane & Marder, 1993). Sedation could then be achieved by the addition of a benzodiazepine such as lorazepam.

For all newly diagnosed patients, the choice of typical antipsychotic is in itself a matter of personal preference and experience. It should be borne in mind that there is little evidence supporting the use of poly-pharmacy (Thompson, 1994) and that using a single neuroleptic for an entire therapeutic trial ensures that the patient receives the treatment most likely to produce symptomatic relief in the shortest time. Careful thought must therefore be given to the use of neuroleptics such as droperidol, which is not licensed for long-term maintenance treatment.

The advent of atypical antipsychotics with unrestricted licenses, such as risperidone, sertindole and olanzapine, may revolutionise the treatment of first-onset psychoses. Although further research

is needed, a case can be made for all newly diagnosed schizophrenics who will take oral medication to receive one of the atypical antipsychotics as first-line treatment. These drugs exhibit reduced rates of neurological side-effects in comparison with typical antipsychotics at therapeutic doses (Casey, 1996). They are equally effective in comparison with typical antipsychotics and may share with clozapine reduced rates of tardive dyskinesia and enhanced efficacy against secondary negative symptoms.

Optimum doses of atypical antipsychotics is still an area of debate. It has been suggested that the optimum dose for risperidone is 6–8 mg/day (Marder, 1994). Olanzapine and sertindole are still under scrutiny and the doses outlined in their respective data sheets should be followed.

Medium-term treatment

This is the time from the expectation of first treatment response to the point at which the patient may be considered a responder or non-responder to a medication. The dose and duration of a medication that a patient should receive before a change is considered is still a source of some debate; however, there are some guidelines. Treatment resistance is usually defined as lack of satisfactory clinical improvement despite the use of two antipsychotics from different chemical classes prescribed at an adequate dose for an adequate duration. Stricter criteria may be adopted, as in the Kane Criteria. The patient should be treated for >6 weeks at a minimum dosage of >500 mg chlorpromazine equivalents per day. If satisfactory improvement has not occurred, then switch to a drug of different chemical class for a further six weeks. If again there has been a poor response, clozapine treatment should be seriously considered.

With the advent of the Clozaril Patient Monitoring Service, the risks associated with clozapine-induced agranulocytosis have been minimised. In addition, the need for early use of clozapine in treatment resistance is becoming more clear. As already discussed, the pattern of illness is established early for the majority of patients. Up to a third of patients receiving standard neuroleptics will be resistant to such treatment. If the supposition that psychosis itself is toxic is true, then every effort must be made to give patients an effective treatment as early as possible in the course of their illness. Up to a half of treatment-resistant patients will respond to clozapine (for review see Wagstaff & Bryson, 1995).

Rehabilitation and psychological therapies should be considered during this phase of

treatment, carrying over into the long-term treatment phase. Rehabilitation should focus on four key areas: the need for comprehensive and long-term therapy; individually tailored treatment programmes based on individual needs; active participation in treatment by patient and family; and possible limitations that the patient may suffer as a direct result of their illness (Bellack & Mueser, 1993). As with any rehabilitation programme, the aim should be to maximise the patient's strengths and help to redevelop their abilities. In view of the correlation between social isolation and increased relapse rates, social skills training has an important part to play in any rehabilitation. As most patients return to their families after a hospital stay, it is surprising that there has not been greater enthusiasm for the use of family intervention strategies. A variety of modes of intervention have been shown to have a robust effect on relapse prevention. Most of these methods involve family education, improving communication, 'here and now' problem-solving and attempts at helping emotional processing within families (Kuipers, 1996). A combination of social skills training with family education and medication may significantly reduce subsequent relapse rates, in comparison with any other combination (Hogarty *et al*, 1991).

Recent research has indicated the usefulness of CBT in schizophrenia. Therapy centres around enhancing coping strategies, goal-setting and the modification of hallucinations and delusions. This is particularly indicated to promote psychological adjustment and insight and for patients who have medication-resistant hallucinations and delusions. CBT has also been advocated in the treatment of acute psychosis (Drury *et al*, 1996a,b)

Long-term maintenance treatment

The use of maintenance antipsychotics for first-onset schizophrenia is an under-researched area. Studies focusing on prophylactic antipsychotic medication in chronic schizophrenia have shown an almost 75% 6–24 month relapse rate in patients who were switched to placebo after a year symptom-free. This is in contrast to a relapse rate of 23% in patients on continuous antipsychotic medication (Hegarty *et al*, 1994). Recent research in similar populations has shown that effective prophylaxis can be achieved with doses of typical antipsychotic medication lower than the standard prescribed dose, provided this is combined with relatively close follow-up. There was also a corresponding reduction in side-effects and negative symptoms

in the low-dose groups (for review see Carpenter & Carpenter, 1996). The use of low-dose depot medication (as opposed to oral medication) may have additional benefits in terms of relapse prevention (Davis *et al*, 1994).

It would seem logical that in well-characterised patients with a first diagnosis of schizophrenia similar clinical issues will dictate prescribing practice, and that these rates will be mirrored, at least in part. Unfortunately, few prospective studies in newly diagnosed cohorts have been reported.

It is still unclear how long effective treatment should be continued after the first onset of schizophrenia. In view of the consistent finding that at least a quarter of first-episode patients recover without subsequent relapse, it would seem sensible to limit the amount of time that newly diagnosed patients spend on medication, for fear of causing unnecessary harm to a substantial minority of patients who do not require prophylactic medication. There is, as yet, no convincing body of evidence to allow a clear decision, although the literature does indicate that first-episode patients gain the maximal benefit from neuroleptic therapy after about six months of treatment (Carpenter & Carpenter, 1996). It would be wise, therefore, to suggest a six-month treatment period at minimum effective dose, followed by a further six months of progressive dose reduction. This would require close clinical supervision, but would be expected to reduce adverse effects and perhaps enhance compliance. Close collaboration with the patient over medication doses and strategies may also enhance their therapeutic engagement and increase the likelihood that they will approach services and accept treatment earlier in the course of a subsequent relapse.

The question of depot medication for first-episode patients is a difficult one. While there is support for enhanced relapse prevention in chronic patients given depot antipsychotics, the generalisability of this to first-episode patients is unclear. At the current level of knowledge, the use of depot neuroleptics for this group should be reserved for patients who have been shown to gain significant clinical benefit from typical antipsychotic medication, but have shown consistent difficulties with compliance.

The use of the novel atypical antipsychotics, risperidone, sertindole and olanzapine, for prophylactic treatment has not yet been fully validated in newly diagnosed or chronic schizophrenic populations. Clozapine, the prototypical atypical antipsychotic, similarly has not been investigated in randomised controlled trials of

maintenance therapy. This is because of the restrictions imposed on its use. However, the clinical efficacy of clozapine in relapse prevention is well established (naturalistically) at 1–2 years of treatment, and there have been naturalistic reports of good maintenance efficacy for up to 17 years of treatment (for review see Wagstaff & Bryson, 1995).

There are several other reasons to make the assumption that novel atypical antipsychotics should be effective in prophylaxis. All antipsychotics so far investigated as part of controlled trials have been shown to be equally effective maintenance treatments. As the atypicals are at least as efficacious as typical antipsychotics in acute treatment, it might follow that they will also be adequate long-term treatments. It may well be that the atypicals will be shown to be better for long-term therapy. Although we still do not know precisely how clozapine exerts its effect, all of the atypical antipsychotics share a high 5-HT_{2A}: striatal D₂ receptor blockade ratio as part of their pharmacodynamic profile. It has been suggested that this is why these drugs exhibit a lower incidence of neurological side-effects and secondary negative symptoms at optimum doses (Kapur & Remington, 1996). It may be hypothesised that if adverse effects and negative symptoms are indeed minimised with the atypical antipsychotics, then compliance and re-hospitalisation rates will be lower than with typical antipsychotic maintenance treatment.

Psychosocial rehabilitation and cognitive psychotherapy are an integral part of long-term maintenance treatment, where appropriate. Family and patient education regarding the ramifications of the patient's illness and the need for treatment has been shown to be effective in reducing subsequent relapse and enhancing the therapeutic relationship between patients, carers and professionals. This may have implications for early recognition and treatment of incipient relapses (for review see Kuipers, 1996). The problem of social isolation should be addressed by encouraging the patient to become involved in locally provided services or rehabilitation resources.

Most recent reviews in this area have made an assertion that one of the best ways of reducing morbidity and hospitalisation for newly diagnosed patients is the early recognition of relapse (Carpenter & Carpenter, 1996; Birchwood *et al*, 1997). Therefore, of overriding importance is the integration of pharmacological and psychosocial treatments in the framework of available care networks. This should strengthen communication and allow a more proactive approach to be taken to treatment needs.

Conclusions

In comparison with the efforts that have been made in biological and epidemiological research in patients with newly diagnosed schizophrenia, prospective studies of treatment have been scarce. Advances in neuropharmacology and psychological therapies should allow a more eclectic and hypothesis-driven approach to research in this area than has hitherto been possible.

The relative importance of the first episode of psychosis in terms of the patients' experience of psychiatric services and treatments cannot be over-emphasised. The evidence that delaying effective treatment will reduce the extent of future remission provides an impetus to the need for clear guidelines over the pharmacological and psychosocial management of the newly diagnosed patient with schizophrenia.

A framework for the medication treatment of a newly diagnosed patient with schizophrenia is summarised in Box 2.

Although this (or any other) framework remains to be evaluated in a randomised controlled trial, the pharmacotherapy of schizophrenia has developed markedly over the past decade. The confirmation that reduced doses of typical

antipsychotics are therapeutically effective has already begun to alter prescribing practices in the UK. The re-introduction of clozapine, the advent of risperidone, sertindole and olanzapine, and the imminent arrival on the market of other novel atypical antipsychotics such as quetiapine and ziprasidone, promise great hope for the future of schizophrenia treatment. This optimism is reinforced by the increasingly evidence-based use of effective psychosocial treatments for schizophrenia. However, without a treatment consensus based on well-conducted trials, the benefits seen with these treatments are likely to be patchy at best, and the ability of clinical psychiatrists to justify resource allocation requirements will be severely impaired.

References

- Angrist, B. & Shulz, S. C. (eds) (1990) *Introduction to the Neuroleptic Non-Responsive Patient: Characterization and Treatment*. Washington, DC: American Psychiatric Press.
- Bellack, A. S. & Mueser, K. T. (1993) Psychosocial treatment for schizophrenia. *Schizophrenia Bulletin*, **19**, 317–336.
- Birchwood, M., McGorry, P. & Jackson, H. (1997) Early intervention in schizophrenia. *British Journal of Psychiatry*, **170**, 2–5.
- Carpenter, W. T. & Carpenter, W. T., Jr. (1996) Maintenance therapy of persons with schizophrenia. *Journal of Clinical Psychiatry*, **57** (suppl. 9), 10–18.

Box 2. Pharmacological treatment

Acute phase

Use of a typical or atypical antipsychotic at a therapeutic dose (roughly 500 mg chlorpromazine equivalents/refer to manufacturers' data sheets for atypical neuroleptics)

Benzodiazepines (rather than high-dose neuroleptics) for sedation (i.e. lorazepam 2–4 mg, diazepam 5–10 mg)

Medium term

Six weeks' treatment on drug of first choice at doses of 250–750 mg chlorpromazine equivalents (refer to manufacturers' data sheets for doses of atypical neuroleptics)

If this is ineffective, then six weeks' treatment on a medication of a different chemical class at similar dose equivalents

If this is ineffective, then consider the patient for treatment with clozapine

Long-term maintenance

Maintenance on first effective antipsychotic at minimal therapeutic dose for six months

Slow reduction of medication over six months with close clinical review

If there are residual deficits but acceptable clinical improvement, then consider longer-term maintenance

If the patient relapses, then restart medication at full therapeutic dosage

If the patient requires clozapine, then it is unlikely that any attempt to stop medication in the future will be successful

- Casey, D. E. (1996) Extrapyramidal syndromes and new antipsychotic drugs: findings in patients and non-human primate models. *British Journal of Psychiatry*, **168** (suppl. 29), 32–39.
- Crow, T. J., MacMillan, J. F., Johnson, A. L., et al (1986) A randomised controlled trial of prophylactic neuroleptic treatment. *British Journal of Psychiatry*, **148**, 120–127.
- Davis, J. M., Metalon, L., Watanabe, M. D., et al (1994) Depot antipsychotic drugs: place in therapy. *Drugs*, **47**, 741–773.
- Drury, V., Birchwood, M., Cochrane, R., et al (1996a) Cognitive therapy and recovery from acute psychosis: a controlled trial. I: Impact on psychotic symptoms. *British Journal of Psychiatry*, **169**, 593–601.
- , —, —, et al (1996b) Cognitive therapy and recovery from acute psychosis: a controlled trial. II: Impact on recovery time. *British Journal of Psychiatry*, **169**, 602–607.
- Frances, A. J. & Weiden, P. (1987) Promoting compliance with outpatient drug treatment. *Hospital and Community Psychiatry*, **38**, 1158–1160.
- Goldberg, T. E., Hyde, T. M., Kleinman, J. E., et al (1993) Course of schizophrenia: neuropsychological evidence for a static encephalopathy. *Schizophrenia Bulletin*, **19**, 797–804.
- Harrison, G., Croudace, T., Mason, P., et al (1996) Predicting the long term outcome of schizophrenia. *Psychological Medicine*, **26**, 697–705.
- Hegarty, J. D., Baldessarini, R. J., Tohen, H., et al (1994) One hundred years of schizophrenia: a meta-analysis of the outcome literature. *American Journal of Psychiatry*, **151**, 1409–1416.
- Helgason, L. (1990) Twenty years' follow-up of first psychiatric presentation for schizophrenia: what could have been prevented? *Acta Psychiatrica Scandinavica*, **81**, 231–235.
- Hogarty, G. E., Anderson, C. M., Resii, D. J., et al (1991) Family psychoeducation, social skills training and maintenance chemotherapy in the aftercare treatment of schizophrenia. II: Two year effects of a controlled trial on relapse and adjustment. *Archives of General Psychiatry*, **48**, 340–347.
- Inoue, K., Nakajima, T. & Kato, N. (1986) A longitudinal study of schizophrenia in adolescence. I: The one to three year outcome. *Japanese Journal of Psychiatry and Neurology*, **40**, 143–151.
- Johnstone, E. C., Crow, T. J., Johnson, A. L., et al (1986) The Northwick Park Study of first episodes of schizophrenia. I: Presentation of the illness and problems relating to admission. *British Journal of Psychiatry*, **148**, 115–120.
- Kane, J. M. & Marder, S. R. (1993) Psychopharmacological treatment of schizophrenia. *Schizophrenia Bulletin*, **19**, 287–302.
- Kapur, S. & Remington, G. (1996) Serotonin-dopamine interaction and its relevance to schizophrenia. *American Journal of Psychiatry*, **153**, 466–476.
- Kuipers, E. (1996) The management of difficult to treat patients with schizophrenia, using non-drug therapies. *British Journal of Psychiatry*, **169** (suppl. 31), 41–51.
- Lo, W. H. & Lo, T. (1977) A ten-year follow-up study of Chinese schizophrenics in Hong Kong. *British Journal of Psychiatry*, **131**, 63–66.
- Loebel, A. D., Lieberman, J. A., Alvir, J. M. J., et al (1992) Duration of psychosis and outcome in first-episode schizophrenia. *American Journal of Psychiatry*, **149**, 1183–1188.
- Malhotra, A. K., Litman, R. E. & Pickar, D. (1993) Adverse effects of antipsychotic drugs. *Drug Safety*, **9**, 429–436.
- Marder, S. R. (1994) Risperidone in the treatment of schizophrenia. *American Journal of Psychiatry*, **151**, 825–835.
- McGlashan, T. H. & Johannessen, J. O. (1996) Early detection and intervention with schizophrenia: rationale. *Schizophrenia Bulletin*, **22**, 201–222.
- Moscarelli, M., Capri, S. & Neri, L. (1991) Cost evaluation of chronic schizophrenic patients during the first three years after first contact. *Schizophrenia Bulletin*, **17**, 421–426.
- Opjordsmoen, S. (1991) Long-term clinical outcome of schizophrenia with special reference to gender differences. *Acta Psychiatrica Scandinavica*, **83**, 307–313.
- Rabiner, C. J., Wegner, J. T. & Kane, J. M. (1986) Outcome study of first episode psychosis: relapse rates after 1 year. *American Journal of Psychiatry*, **143**, 1155–1158.
- Szymanski, S. R., Cannon, T. D., Gallacher, F., et al (1996) Course and treatment response in first episode and chronic schizophrenia. *American Journal of Psychiatry*, **153**, 519–525.
- Thara, R., Henrietta, M., Joseph, A., et al (1994) Ten-year course of schizophrenia – the Madras longitudinal study. *Acta Psychiatrica Scandinavica*, **90**, 329–336.
- Thompson, C. (1994) The use of high-dose antipsychotic medication. *British Journal of Psychiatry*, **164**, 448–458.
- Wagstaff, A. J. & Bryson, H. M. (1995) Clozapine: a review of its pharmacological properties and therapeutic use in patients with schizophrenia who are unresponsive to or intolerant of classical antipsychotic agents. *CNS Drugs*, **4**, 370–400.
- Wyatt, R. J. (1991) Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, **17**, 325–351.

Multiple choice questions

- For newly diagnosed patients with schizophrenia:
 - the longer the duration of prodromal symptoms the longer the time to remission
 - duration of illness predicts frequency of relapse in the first two years after diagnosis
 - these patients tend to have impairments in neuropsychological functioning which change little over time
 - lower level of remission is associated with lower social class
 - the first two years of the illness appear to predict the chronic course of that illness.
- The efficacy of the following in long-term maintenance treatment of schizophrenia has been proven:
 - droperidol
 - olanzapine
 - chlorpromazine
 - fluphenazine decanoate
 - haloperidol.
- In relation to treatment resistance:
 - a patient should be continued on a neuroleptic for six months before a decision can be made about treatment resistance
 - up to one-half of treatment-resistant patients will respond to clozapine
 - doses of neuroleptics of >750 mg/day chlorpromazine equivalents are associated with enhanced antipsychotic efficacy
 - if a patient is resistant to a single neuroleptic after six weeks of treatment, another neuroleptic from a different chemical class should be added
 - low-dose haloperidol is as efficacious as clozapine in treatment-resistant patients.
- Regarding the treatment of first-onset schizophrenia:
 - sedation in the agitated patient is best achieved by increasing the dose of neuroleptic

- b family intervention strategies are unlikely to be of use
- c the maximum benefit from a given neuroleptic is reached after about six months of treatment
- d the optimum dose of risperidone is between 8 and 12 mg/day
- e cognitive-behavioural therapy may be effective against delusions and hallucinations.

MCQ answers			
1	2	3	4
a F	a F	a F	a F
b T	b F	b T	b F
c T	c T	c F	c T
d F	d T	d F	d F
e T	e T	e F	e T