

Concept and Management of Treatment Resistant Schizophrenia (TRS)

Nitesh Painuly¹, Nitin Gupta², Ajit Avasthi*³

ABSTRACT

Treatment resistance in schizophrenia is a fairly common problem faced by psychiatrists worldwide. The concept and definition of Treatment Resistant Schizophrenia (TRS) is still far from satisfactory. Data suggests the presence of biological factors underlying TRS. Second generation antipsychotics are advocated for patients with TRS. However, till date, clozapine remains the treatment of choice. Evidence for other pharmacological measures and ECT is accumulating. Psychosocial interventions do form an integral component of management of TRS. It can be concluded that, with advances in psychopharmacology, TRS needs to be better researched and managed in the future.

Key Words : Schizophrenia, treatment resistant, clozapine, atypical antipsychotics, difficult to treat schizophrenia.

Introduction

One fifth to one third of all patients with schizophrenia are resistant to drug treatment (Conley and Kelly, 2001). Management of such patients remains a persistent public health problem. Patients with Treatment Resistant Schizophrenia (TRS) are found highly symptomatic, require extensive periods of hospitalisation, and comprise a high share of total cost towards treating schizophrenia (McGlashan, 1988; Revicki et al, 1990). Newer antipsychotics, especially after proven efficacy of clozapine in TRS, has given hope for such patients.

TRS: EVOLUTION OF CONCEPT

Patients with schizophrenia are not homogenous due to differing diagnostic criteria, etiopathogenesis, symptomatology, stage of illness and comorbid pathology. Similarly there is marked heterogeneity of response to treatment in different studies depending on the diagnostic and inclusion criteria, target symptoms, and pharmacological and psychosocial treatment applied. Therefore, treatment resistance in schizophrenia is difficult to define and criteria still remain controversial.

Initially, chronic hospitalisation (hospitalisation more than two years) was taken as the criteria for treatment resistance (Small et al, 1975; Carman et al, 1981). This approach did not prove to be of help because a person may be hospitalised

for various other reasons like poor compliance or inadequate psychosocial support, despite having low symptomatology.

Later, considering the good response of positive symptoms to typical antipsychotics, persistent positive symptoms despite adequate drug therapy became the criterion for treatment resistance in schizophrenia. Kane and co workers, in 1988 during their Multicenter Clozapine Trial, used the same concept of Treatment Resistant Schizophrenia (TRS). Their approach however underestimates the importance of symptoms other than the positive symptoms of schizophrenia. Studies are now available which demonstrate that newer antipsychotics are also effective in improving negative and cognitive symptoms (Kane, 1999). Henceforth, it becomes essential that if one wants to assess the treatment response, it has to be assessed in all domains, and not of positive symptoms alone.

Kane (1996) while defining “inadequate treatment response” in schizophrenia also included patients with primary negative symptoms, patients who were intolerant to medication and patients who had “breakthrough” episode while on regular medication, other than patients having persistent positive symptoms.

In clinical settings we do see that treatment response is not a “yes” or “no” kind of phenomenon and very few patients suffering from schizophrenia reach their premorbid level. Considering this, various researchers (May et al, 1988;

¹Senior Resident, Dept. of Psychiatry, PGIMER, Chandigarh – 160 012, India. e-mail : medinst@pgi.chd.nic.in

² Assistant Professor

³Additional Professor

*Correspondence

Brenner et al, 1990) took treatment response on a continuum and gave a dimensional approach to treatment refractoriness.

“Difficult to treat schizophrenia” is another related concept, which includes patients who fail to show response not only to drug therapy but also to psychosocial interventions; violent, aggressive, non-compliant patients; and patients who for some reasons evoke negative response from caregivers including mental health professionals (Kulhara, 1998).

TRS: CRITERIA (Kane et al, 1988)

1. Persistent positive psychotic symptoms: item score > 4 (moderate) on at least 2 of 4 positive symptom items of the Brief Psychiatric Rating Scale (BPRS) (rated on a 1-7 scale) (Overall and Gorham, 1961)-hallucinatory behaviour, suspiciousness, unusual thought content, and conceptual disorganization.
2. Current presence of at least moderately severe illness as rated by the total BPRS score (>4 on the 18-item scale) and a score of >4 (moderate) on the Clinical Global Impression (CGI) scale.
3. Presence of illness: no stable period of good social and/or occupational functioning within the last 5 years (inability to maintain work and relationship).
4. Drug-refractory condition: at least 3 periods of treatment in the preceding 5 years with conventional antipsychotics (from at least 2 chemical classes) at doses equivalent to ≥ 1000 mg per day of chlorpromazine of 6 weeks each, without significant symptom relief, and failure to improve by at least 20% in total BPRS score or intolerance to a 6 week prospective trial of haloperidol at a dose of 10-60 mg per day.

CRITERIA FOR TRS: CRITIQUE

Categorical Vs Continuum Approach

Full remission from an episode of schizophrenia is unusual and most patients are at best partial responders (Meltzer, 1990). Response evaluation will also take into account whether the persistent symptoms are positive, negative, cognitive or affective in nature. An alternative, more liberal definition of treatment refractoriness, proposed by Meltzer (1990) is the failure of patients to return to their best premorbid level of functioning. But the disadvantage of this approach was that all partial responders were considered equal and further, not qualitatively different from patients

who were completely refractory. Brenner et al (1990) recommended conceptualisation of a continuum of response refractoriness to antipsychotic medication. They described seven levels of response ranging from full clinical remission to severely refractory. Addressing the controversy between categorical and continuum approach, Peuskens (1999) concluded that the dichotomous definition of TRS may be a useful approach for research. However, it does not fully appreciate the impact of residual symptoms and psychosocial problems and will underestimate the number of partially and poorly responding patients.

Symptom profile in TRS

Resistance to positive symptoms increases over time, in contrast negative and cognitive symptoms are usually present from the first episode (Meltzer et al, 1998). Additionally, impairment in cognitive function contributes to poor long term outcomes for patients of schizophrenia (Conley and Kelly, 2001). Drugs shown to be effective in TRS (clozapine, risperidone) have demonstrated efficacy in reducing negative and cognitive symptoms, but there is controversy regarding whether these drugs truly treat primary negative symptoms or whether their effect is associated with secondary benefits on depressive, extrapyramidal, or positive symptoms (Meltzer, 1994; Lieberman et al, 1994).

TRS: Duration Criteria

Persistence of illness for more than 5 years was taken as the duration criteria for TRS by Kane et al (1988). This was most probably the impact of serious side effects of clozapine (drug induced agranulocytosis), which made researchers so stringent about duration criteria. On the other hand clinical history of persistent psychosis for at least 2 years is found to be sufficient for TRS (Brenner et al, 1990). Even some researchers have mentioned that one year of unresponsiveness to treatment may be an adequate time period (Peuskens, 1999).

TRS: Adequate Drug Trial

The fact that there was only a 3% response rate to prospective haloperidol treatment and a 4% response rate to double blind chlorpromazine treatment in the Multicenter Clozapine Trial led to the belief that failure of two retrospective drug trials would be as effective as 3 in screening for treatment resistance (Kane et al, 1988). Kinon et al (1993) mentioned that subjects who do not respond to 2 adequate antipsychotic trials (1 retrospective and 1 prospective) have less than 7% chance of responding to

another trial. The FDA guidelines on clozapine use state that a patient before being treated with clozapine should have failed to respond to two separate trials of antipsychotics. Thus, two drug trial failures are generally accepted as the criterion for treatment resistance.

The evidence that second generation antipsychotics are somewhat more effective than traditional medications has opened the question of the type of the drug patient should fail (Marder, 1996). Most clinicians agree that failure to respond to second generation antipsychotics should precede a clozapine trial (Smith and Docherty, 1998). It is generally recognized that a four to six week period (rather than a strict 6-week period) is adequate for a treatment trial (Kane and Marder, 1993).

Recommended dosage ranges have also been revised. Initially at least 1000 mg per day of chlorpromazine (or its equivalent) was the proposed dose for use during a conventional antipsychotic trial. However, doses greater than or equal to 400 mg of chlorpromazine adequately block 80% to 90% of dopamine receptors (Farde et al, 1992). It has been additionally reported that higher doses produce no direct therapeutic benefit even in patients who are nonresponsive to therapy (Kinon et al, 1993) and do not improve efficacy in acute treatment (VanPutten et al, 1990).

Kane et al (1988) in their Multicenter Clozapine Trial defined treatment response as 20% or more decrease in total BPRS score, and final score of 36 or less. Conley and Buchanan (1997) modified the treatment response criteria as 20% or more decrease in total BPRS and final score of 36 or less or drop on another scale usually to a score equivalent to mild psychosis. Meltzer (1990) took treatment responsiveness on a continuum. This seems appropriate for clinical settings.

TRS: ETIOPATHOGENESIS

Certain neurodevelopmental factors have been found to be associated with poor treatment response as shown in table 1.

If we go by the neurodegenerative pathology of schizophrenia, it has been found that some patients worsen over the course of the illness either because of its progression or because they become less responsive to treatment (Wyatt, 1991).

Similarly, duration of untreated psychosis was found to be a strong predictor of future relapse, longer course and incomplete recovery in patients with schizophrenia (Crow

TABLE 1 :
Neurodevelopment factor and poor treatment response

Factor(s)	Author
Lower level of premorbid functioning, presence of deficit state, male gender, cavum septum pellucidum	Murray et al, 1992
High prevalence of obstetrical complication	Weinberger, 1995
Lateral and third ventricle enlargement	Lieberman et al, 1993
Vulnerability to tardive dyskinesia	Chakos et al, 1996

et al, 1986). Miller and Chouinard (1993) proposed loss of cholinergic neurons as a cause for treatment resistance in schizophrenia. It was found that conventional antipsychotics acting at D2 receptors produce their therapeutic effect indirectly by action on the cholinergic interneurons, followed by reduction of firing of dopamine neurons themselves. This in turn reduces the dopaminergic activation of D1 receptors. Loss of cholinergic interneurons prevents standard neuroleptic drugs from having their therapeutic effect. On the other hand, drugs acting by blocking the D1 receptors e.g. clozapine should still be able to exert a direct effect and improve the so-called ‘drug resistant positive symptoms’.

TRS: EPIDEMIOLOGY

In early antipsychotic trials (Cole et al, 1966; Klein and Devis, 1968) approximately 30% of schizophrenic patients derived little, if any, benefit from medication. Clinical trials done in 1990’s (Levinson et al, 1990; McEvoy et al, 1991; Kinon et al; 1993) showed that only 50% of patients showed a good response to conventional antipsychotics. This raises the question whether response to medication has declined over past three decades. Kane et al (1996) proposed that change in nosology with a tendency to overdiagnose schizophrenia and underdiagnose affective illness in 1960’s, increasing prevalence of substance abuse among patients and current policy of limited hospitalisation could be some of the reasons for this trend. Hegarty et al (1994) conducted a meta- analysis of 20th century literature on outcome of schizophrenia and concluded that despite widespread use of neuroleptic drugs and other contemporary treatments, a shift had occurred towards poorer outcome in the last decade.

TABLE 2 :

Prevalence of TRS

Study	Prevalence of treatment resistance in patients with schizophrenia	Remarks
Terkelsen and Grosser (1990)	18% of inpatients 25% of outpatients	More stringent criteria than current FDA guidelines. No assessment for adequacy of prior medications trial
Juarez-Reyes et al (1995)	43% (n=293)	Patients of tardive dyskinesia were also included.
Essock et al (1996)	60% (n=1300)	Extrapolated from their data that on any given day in US country and state hospitals approximately 40,000 patients would meet eligibility criteria for clozapine

Prevalence of TRS: Clozapine Related Studies

One strategy for examining the epidemiology of treatment resistance in schizophrenia is to apply the eligibility criteria for clozapine treatment to specific populations. Till date three studies were available (Table 2).

MANAGEMENT OF TRS**TRS: DRUG THERAPY****(a) Conventional Antipsychotics**

A number of studies have examined the effect of high dose typical antipsychotics in patients who are poor or partial responders but found little conclusive advantage (Quitkin et al, 1975). In controlled trials in patients with drug-resistant symptoms, fewer than 5% responded after therapy was changed from one conventional antipsychotic to another (Kane et al, 1988; Breier et al, 1993). Kinon et al (1993) found that there is no advantage of increasing the dose, changing to another medicine or prolonging treatment. On the other hand, Shalev et al (1993) observed further improvement with specific alternatives of prior conventional antipsychotic treatment administered over a period of time longer than 4 to 8 weeks.

(b) Second Generation Antipsychotics**CLOZAPINE**

Though some anecdotal reports and clinical trials (Claghorn et al, 1987) had suggested that clozapine might be effective in TRS, the most definitive evidence of its effectiveness came from a multicenter trial (Kane et al, 1988) in which clozapine was compared with chlorpromazine. Thirty

percent of clozapine patients met improvement criteria (as compared to 4% chlorpromazine treated patients) after a 6 week trial. Breier et al (1993) and Schooler et al (1997) indicate that higher proportion of TRS patients (up to 60%) will meet stringent improvement criteria if the trial period is extended to a longer period (up to 29 weeks). It has been suggested that clozapine may be helpful in a broader population of TRS patients, including patients living in the community (Schooler et al, 1997). As per current understanding, clozapine is the only drug with proven efficacy in rigorously defined TRS and undoubtedly superior to conventional antipsychotics in this population (Chakos et al, 2001). On the other hand, in a recent meta-analysis, Moncrieff (2003) addressed the issue of heterogeneity in clozapine related study and found that recent large studies have not found a clinically relevant advantage for clozapine. Meta-regression showed that shorter study duration, financial support from a drug company and higher baseline symptom score consistently predicted greater advantage of clozapine. Females, patients having higher mean metabolic ratio, and lesser fall in total white cells and neutrophils after institution of clozapine were found the good predictor of response (Mauri et al, 2003). Temporal grey matter volume and metabolism, metabolic activity in thalamus, pallidum/putamen and caudate nucleus correlated with improvement in positive symptoms, whereas patients with high baseline dorsolateral prefrontal volume and metabolic activity were more likely to experience improvement in negative symptoms. Improvement in disorganised symptoms was inversely correlated to total intracranial volume and hippocampal volume (Molina et al, 2003). Significantly more number of patients with cognitive disorganisation were found among nonresponders and patients with behavioural disorganisation were found more among partial responders to clozapine (Rodriguez et

al, 1998). Improvement with clozapine is mainly documented in positive symptoms, affective symptoms, suicidal behaviour and frequent hospitalisations (Schatzberg et al, 2003).

RISPERIDONE

There were early reports of (Chouinard et al 1994; Keck et al 1995) some response with risperidone but these studies were open label, retrospective, or not controlled. Risperidone has also been found to have favourable effect on ability to accurately perceive emotions and verbal working memory in patients with TRS (Green et al, 1997; Kee et al, 1998). A well controlled, double blind study by Wirshing et al (1999) showed that risperidone is more effective and better tolerated than haloperidol in TRS. Risperidone showed similar efficacy to clozapine in a few studies (Klieser et al, 1995; Bondolfi et al, 1998) but TRS criteria were poorly defined and the sample size was small. Clozapine was found to have superior efficacy than risperidone (Azorin et al, 2001) and risperidone treatment was not found to be effective in clozapine responders (Lacey et al, 1995; Shore, 1995).

OLANZAPINE

There have been several open reports of possible efficacy with olanzapine in treatment resistant patients (Martin et al, 1997; Thomas and Labbate, 1998; Dossenbach et al, 2000) but the inclusion of less stringently defined patient population in some of these studies has been of concern. Double blind and open label studies show that olanzapine is more effective than conventional antipsychotics, but it is not as effective as clozapine (Conley et al, 1998; Sanders and Mossman, 1999; Breier and Hamilton, 1999). Furthermore, olanzapine resistant patients respond to subsequent trial of clozapine at about the rate that would have been expected in any other treatment resistant group (Conley et al, 1999).

OTHER SECOND GENERATION ANTIPSYCHOTICS

Studies on efficacy of other second-generation antipsychotics in TRS are lacking. Quetiapine has been found beneficial in partially responding patients with schizophrenia (Emsley et al, 2000). However no controlled trials in strictly defined TRS patients have been published.

Recently, Chakos et al (2001) conducted a meta-analysis based on 12 controlled studies in patients with TRS. Results indicated that clozapine exhibited superiority over typical antipsychotics in terms of both efficacy and safety with a

moderate (0.48) effect size, clozapine treated patients are 2.45 times and olanzapine treated patients are 1.71 times more likely to meet categorical response criteria as compared to typical antipsychotics, fewer extra pyramidal side effects with clozapine and olanzapine, and study completion rate was maximum for risperidone (84.8%), followed by clozapine (69.6%) and least for typical antipsychotics (56.1%).

(c) Alternate (adjunct) therapies

If patients remain resistant to treatment after a clozapine trial or cannot take clozapine, alternate therapies should be considered (Miller et al, 1999).

LITHIUM

Adjunct lithium therapy was found beneficial in some patients with TRS (Small et al, 1975; Carman et al, 1981). A 4-week trial is adequate to determine response. Response was more prominent in patients with affective symptoms (Delva and Letemendia, 1986). There are reports that lithium reduces violent behaviour in TRS patients (Christison et al, 1991). Published trials of adjunct lithium therapy, though positive, have been conducted with small number of patients and the criteria used for defining TRS are not clear or over inclusive (Kane, 1996). More recent reports have found no benefit with adjunct lithium therapy (Schulz et al, 1999). Therefore, definitive evidence on the benefit of lithium is yet not present. Lithium should be used with caution in combination with clozapine and other antipsychotics because of the increased risk of neurotoxicity including delirium (Barnes and McEvedy, 1996; Small et al, 2003). A relatively low dosages of lithium (300-900 mg/day) as adjunct is recommended (Jones and Thompson, 1995).

ANTICONVULSANTS

Controlled trials with adjunct carbamazepine and valproic acid in TRS have shown positive results (Schulz et al, 1990; Wassef et al, 2000). However these trials enrolled fewer subjects, the positive effects noted were modest and usually involved non-specific improvement in areas such as behaviour and social adjustment. A meta-analysis done by Leucht et al (2002) concluded that carbamazepine, as an augmentation strategy in schizophrenia cannot be recommended for routine use except for patients with excitement and aggression. Carbamazepine should not be used in combination with clozapine due to increased risk of agranulocytosis (Conley and Kelly, 2001). A few cases of adjunct use of lamotrigine with clozapine with positive results in TRS have also been reported (Dursun and Deakin, 2001).

A review (Hosak and Libiger, 2002) on role of adjunct antiepileptics in schizophrenia mentions that carbamazepine is effective in affective symptoms of schizophrenia and influences violent behaviour in psychotic patients, valproate treatment leads to a decrease in positive symptoms as well as hostility and lamotrigine is expected to influence the positive, negative, affective, and cognitive symptoms of schizophrenia. Topiramate has also been found to be effective in TRS as an adjunct, especially in negative symptoms and clozapine induced weight gain (Dursun and Devarajan, 2000; Drapalski et al, 2001). In most of the studies of TRS, anticonvulsants have been used in their usual antiepileptic dosage (Hosak and Libiger, 2002).

BENZODIAZEPINES

There have been several reports on the use of benzodiazepines in TRS. Results have been mixed with some double blind studies showing a positive effect (Lingiaerde et al, 1979; Wolkowitz et al, 1992) whereas other studies have shown negative results (Ruskin et al, 1979; Pato et al, 1989). Because patients with schizophrenia often have anxiety and irritability, it is not surprising that benzodiazepines are useful in the treatment of this disorder. A high dose of adjunct benzodiazepine reduces positive symptoms, anxiety and agitation (Hosak and Libiger, 2002) and prefrontal cortex atrophy has been found to predict the positive response of the benzodiazepine augmentation in TRS (Seeley et al, 2002).

ELECTROCONVULSIVE THERAPY (ECT)

There is little evidence that ECT alone can alter the chronic symptoms (both positive and negative) of schizophrenia, but in short-term trials, when added to antipsychotic medications for TRS, it has demonstrated favourable response (Conley and Kelly, 2001; Goswami et al, 2003). Up to 20 bilateral ECTs are given before labelling patient unresponsive to ECT. Male sex, paranoid type, younger age, shorter duration of illness and shorter duration of current episode, less family history and higher pre-treatment functioning were found among good predictors of response (Chanpattana et al, 1999). Improvement is found more in positive symptoms than negative ones but beneficial effect was short lived and significant proportion of patients relapsed after two to six months of stoppage of ECT (Sajatovic and Meltzer, 1993; Kales et al, 1999; Chanapattana et al, 1999). Very few studies are available on continuation or maintenance ECT in TRS and found ECT in combination with antipsychotics more effective in preventing relapse as compared to ECT or antipsychotic alone (Chanpattana, 2000; Chanpattana et al, 1999). Improvement on

maintenance ECT in TRS is reported in self injurious behavior, less hospitalisation and better functioning (Dean,2000). A literature review by Tharyan (2000) reports that about 20% patients have improvement with ECT in combination with clozapine. Combined treatment of clozapine with ECT appears to be safe and well tolerated (Kales et al, 1999; Tharyan, 2000). Combination of clozapine with ECT has been proposed as a promising initiation therapy in severely disturbed and non-compliant patients with TRS for rapid treatment response and consequently improved compliance (James and Gray, 1999).

There is very limited evidence for other augmentation strategies i.e. beta blockers, calcium channel blockers , reserpine, glycine and d-cycloserine having any role in TRS and cannot be recommended at present (Hollister and Trivino, 1999; Conley and Kelly, 2001; Schatzberg et al, 2003).

COMBINED ANTIPSYCHOTIC THERAPY (CAT)

While clinical use of CAT in TRS is growing, little research is available to support this treatment approach (Stahl, 1999). The most consistent data so far has come mostly from case reports and open trial studies. Positive results have been found in combination of clozapine with risperidone (Raskin et al, 2000; Taylor et al, 2001), olanzapine (Gupta et al, 1998), pimozide, loxapine and sulpiride (Mowerman and Siris, 1996; Friedman et al, 1997). There is a report of the combined use of risperidone and olanzapine with success (Lerner et al, 2000). There is one well controlled, double blind study showing a positive effect with adjunctive sulpiride therapy in clozapine partial responders (Shiloh et al, 1997). While CAT is rising, there is little controlled work and these preliminary findings needs to be validated.

Regarding practical guidelines for pharmacotherapy in TRS, clozapine remains the gold standard for these patients. A fair and adequate trial (maximum dose up to 900 mg/day for minimum six months) should be given before moving to other less effective and partially understood measures. At next stage another antipsychotic (preferably low dose high potency typical antipsychotic) or other adjunct (lithium or other mood stabilizers, benzodiazepines) can be added. ECT always remains an option for acute exacerbation and maintenance ECT in combination with clozapine can be considered at a stage when initial response with ECT is found to be good and none other treatment seems to work. If patient does not tolerate clozapine or he does not show any response to it, then another atypical antipsychotics can be tried.

TRS: PSYCHOSOCIAL MANAGEMENT

INDIVIDUAL PSYCHOTHERAPY

Specifically regarding TRS, most studies have been done on cognitive behaviour therapy (CBT). Garety et al (2000) in their review of available randomised controlled studies conclusively remarked that, CBT has significant benefits in terms of symptom reduction (especially positive symptoms). The predictors of good outcome are cognitive flexibility and less negative symptoms, with no role of intelligence and severity of psychotic symptoms, and the benefits are sustained up to 1-year post treatment follow-up.

Other than CBT, supportive psychotherapy in the form of a supportive relationship that consists of friendship, advice, practical help in securing financial and supportive services, and vocational counselling has been advised for these medication resistant patients (Torrey, 1986).

Rosberg and Stunden (1990) argued that patients with schizophrenia are often labelled treatment resistant because the psychological treatment they receive is seldom appropriate for their needs. They further said that the main problem in treating schizophrenia with psychotherapy is not the treatment resistant patient but the treatment resistant therapist.

FAMILY INTERVENTIONS

Psycho-educational interventions with families of patients with schizophrenia have a well-established literature support. Behavioural family management is effective in reducing relapses and readmission rates (Leff et al, 1989, 1990). Family interventions reduce burden of care, improve patient's functioning in social areas and are cost-effective (Falloon et al, 1982, 1985; Tarrier et al, 1988, 89, 91, 94). McFarlen et al (1995) and Telles et al (1995) have shown beneficial effects of family interventions in managing treatment resistant patients in the community setting.

COMMUNITY BASED INTERVENTIONS

The broad aim of community-based interventions in TRS is to improve quality of life, stabilize mental health, and minimize relapses and rehospitalizations. Programs included for such patients are "Early symptoms and signs monitoring" so as to recognize early symptoms of relapse (Birchwood and Shepherd, 1992), "Assertive Outreach Programme" - a staff intensive programme aimed at delivery of services in an aggressive and assertive manner (Wykes and Carson,

1996) and crisis intervention which can reduce rehospitalizations and benefit the patient clinically and socially (Muijen et al, 1992).

Conclusion

Treatment resistance in schizophrenia is a concept that still holds different positions in clinical settings and in research areas. While categorical and criteria based approach with more emphasis on positive symptoms is preferred for research, individualised and holistic view for treatment resistance seems appropriate for day to day clinical situations. Regarding pharmacological treatment of TRS, till now only clozapine has demonstrated conclusive and favourable evidence. Other second-generation antipsychotics and adjunct treatment modalities are promising areas but require large sample studies with good methodological framework so as to establish their efficacy. Non-pharmacological interventions, including individual and family therapies, should not be underestimated or underemphasized and should be used to their maximal potential in this special patient population.

References

- Azarin, J.M., Spiegel, R., Remington, G., et al (2001) A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *American Journal of Psychiatry*, 158,1305-1312.
- Barnes, T.R.E. & McEvedy, C.J.B. (1996) Pharmacological treatment strategies in the nonresponsive schizophrenic patient. *International Clinical Psychopharmacology*, 11, 67-71.
- Birchwood, M. & Shepherd, G. (1992) Controversies and growing points in cognitive behavioural interventions for people with schizophrenia. *Psychotherapy*, 20, 305-342.
- Bondolfi, G., Dufour, H., Patris, M., et al (1998) Risperidone versus clozapine in treatment resistant schizophrenia: a randomised double-blind study. *American Journal of Psychiatry*, 155, 499-504.
- Breier, A. & Hamilton, S.H. (1999) Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. *Biological Psychiatry*, 45, 403-411.
- Breier, A., Buchanan, R.W., Irish, D. & Carpenter, W.T. Jr. (1993) Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. *Hospital and Community Psychiatry* 44, 1145-1149.
- Brenner, H.D., Dencker, S.J., Goldstein, M.J., et al (1990) Defining treatment refractoriness in schizophrenia. *Schizophrenia Bulletin*, 16, 551-561.
- Carman, J.S., Bigelow, L.B. & Wyatt, R.J. (1981) Lithium combined with neuroleptics in chronic schizophrenic and schizoaffective patients. *Journal of Clinical Psychiatry*, 42, 124-128
- Chakos, M., Lieberman, J., & Hoffman, E. (2001) Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia : a review and meta-analysis of randomized trials. *American Journal of Psychiatry*, 158, 518-526.
- Chakos, M., Alvir, J.M., Bilder, R. et al (1996) Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. *Archives of General Psychiatry*, 53, 313-319.
- Chanpattana, W. (2000) Maintenance ECT in treatment-resistant schizophrenia. *Journal of Medical Association of Thailand*, 83, 657-662.

- Chanapattana, W., Chakrabhand, M.L., Sackeim, H.A., et al (1999) Continuation ECT in treatment-resistant schizophrenia. *Journal of ECT*, 15, 178-192.
- Chouinard, G., Vainer, J.L., Belanger M.C., et al (1994) Risperidone and Clozapine in the treatment of drug-resistant schizophrenia and neuroleptic induced supersensitivity psychosis. *Progress in Neuropsychopharmacology. Biological Psychiatry*, 18, 1129-1141.
- Christison, G.W., Kirch, D.G. & Wyatt, R.T. (1991) When symptoms persist: choosing among alternative somatic treatments for schizophrenia. *Schizophrenia Bulletin*, 17, 217-245.
- Claghorn, J., Honigfeld, G. & Abuzzahab, F.S. (1987) The risk and benefits of Clozapine vs chlorpromazine. *Journal of Clinical Psychopharmacology*, 7, 377-384.
- Cole, J.O., Goldberg, S.C. & Davis, J.M. (1966) Drugs in the treatment of psychosis: controlled studies. In: Solomon T, ed. *Psychiatric Drugs*. New York, NY: Grollerand Stratton, pp153-180.
- Conley, R.R. & Kelly, D.L. (2001) Management of treatment resistance in schizophrenia. *Biological Psychiatry*, 50, 898-911.
- Conley, R.R., Tamminga, C.A., Kelly, D.L. & Richardson, C.M. (1999) Treatment-resistant schizophrenic patients respond to Clozapine after Olanzapine non-response. *Biological Psychiatry*, 46, 73-77.
- Conley R.R., Tamminga C.A., Bartko J.J. et al. (1998) Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *American Journal of Psychiatry*, 155, 914-920.
- Conley, R.R. & Buchanan, R.W. (1997) Evaluation of treatment resistant schizophrenia. *Schizophrenia Bulletin*, 23, 663-674.
- Crow, T.J., ferrier, I.N. and Johnstone, E.C. (1986) The two syndrome concept and neuroendocrinology of schizophrenia. *Psychiatric Clinic of North America*, 9, 99-113.
- Dean, C.E. (2000) Severe self-injurious behaviour associated with treatment-resistant schizophrenia: treatment with maintenance electroconvulsive therapy. *Journal of ECT*, 16, 302-308.
- Delva, N.J. & Letemendia, F.J. (1986) Lithium treatment in schizophrenia and schizoaffective disorders. In : Kerr A, Snaith P, eds. *Contemporary Issues in Schizophrenia*. London : Royal College of Psychiatrists, pp 381-386.
- Dossenbach, M.R.K., Beuzen, J.N. & Avnon, M. (2000) The effectiveness of olanzapine in treatment-refractory schizophrenia when patients are non responsive to or unable to tolerate clozapine. *Clinical Therapeutics*, 22, 1021-34.
- Drapalski, A.L., Rosse, R.B. & Peebles, R.R. (2001) Topiramate improves deficit symptoms in a patient with schizophrenia when added to a stable regimen of antipsychotic medication. *Clinical Neuropharmacology*, 24, 290-294.
- Dursun, S.M. & Deakin, J.F. (2001) Augmenting antipsychotic treatment with lamotrigine or topiramate in patients with treatment-resistant schizophrenia: a naturalistic case-series outcome study. *Journal of Psychopharmacology*, 15, 297-301.
- Dursun, S.M. & Devarajan, S. (2000) Clozapine weight gain plus topiramate weight loss. *Canadian Journal of Psychiatry*, 45, 198.
- Emsley, R.A., Raniwalla, J., Bailey, P.J. & Jones, A.M. (2000) A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of a demonstrated, partial response to conventional antipsychotic treatment. *International Clinics of Psychopharmacology*, 15, 121-131.
- Essock, S.M., Hargreaves, W.A., Dohm, F.A., et al (1996) Clozapine eligibility among state hospital patients. *Schizophrenia Bulletin*, 22, 15-25.
- Falloon, I.R.H., Boyd, J.L. & McGill, C.W. (1985) Family management in the prevention of morbidity in schizophrenia: Clinical outcome of a two year Longitudinal study. *Archives of General Psychiatry*, 42, 887-896.
- Falloon, I.R.H., Boyd, J.L., McGill, C.W., et al (1982) A family management in the prevention of exacerbations of schizophrenia: a controlled study. *New England Journal of Medicine*, 306, 1437-1440.
- Farde, L., Nordstrom, A.L., Wiessel, F.A. et al (1992) Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and Clozapine: Relation to extrapyramidal side effects. *Archives of General Psychiatry*, 49, 538-544.
- Friedman, A., Adult, K. & Powchik, P. (1997) Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. *Biological Psychiatry*, 42, 522-523.
- Garety, P.A., Fowler, D. & Kulper, E. (2000) Cognitive behavioural therapy for medication-resistant symptoms. *Schizophrenia Bulletin*, 26, 73-86.
- Goswami, U., Kumar, U. & Singh, B. (2003) Efficacy of electroconvulsive therapy in treatment resistant schizophrenia: A double-blind study. *Indian Journal of Psychiatry*, 45, 26-29.
- Green, M.F., Marshall, B.D.Jr, Wirshing, W.C., et al (1997) Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *American Journal of Psychiatry*, 154, 799-804.
- Gupta, S., Sonnenberg, S.J. & Frank, B. (1998) Olanzapine augmentation of Clozapine. *Annals of Clinical Psychiatry*, 10, 113-115.
- Hegarty, J.D., Baldessarini, R.J., & Tohen, M. (1994) One hundred years of schizophrenia: a meta-analysis of the outcome literature. *American Journal of Psychiatry*, 151, 1409-1416.
- Hollister, L.E. & Trevino, E.S. (1999) Calcium channel blocker in psychiatric disorders: a review of the literature. *Candian Journal of Psychiatry*, 44, 658-664.
- Hosak, L. and Libiger, J. (2002) Antiepileptic drugs in schizophrenia: a review. *European Psychiatry*, 17, 371-378.
- James, D.V. & Gray, N.S. (1999) Elective combined electroconvulsive and clozapine therapy. *International Clinical Psychopharmacology*, 14, 69-72.
- Jones, C.A. & Thompson J.W. (1995) Adjunctive treatments in schizophrenia: pharmacotherapies and electroconvulsive therapy. *Schizophrenia bulletin*, 21, 607-619.
- Juaraz-Reyes, M.G., Shumway, M., Battle, C. et al (1995) Effects of stringent criteria on eligibility for clozapine among public mental health clients. *Psychiatric Services*, 46, 801-806.
- Kales, H.C., Dequardo, J.R. & Tandon, R. (1999) Combined electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. *Progress in Neuropsychopharmacology*, 23, 547-560.
- Kane, J.M. (1999) Management strategies for the treatment of schizophrenia. *Journal of Clinical Psychiatry*, 60, (suppl. 12), 13-17.
- Kane, J.M. (1996) Treatment resistant schizophrenic patients. *Journal of Clinical Psychiatry*, 57 (suppl. 9), 35-40.
- Kane, J.M. & Marder, S.R. (1993) Psychopharmacologic treatment of schizophrenia. *Schizophrenia Bulletin*, 19, 287-302.
- Kane, J.M., Honigfeld, G. & Singer, J. (1988) Clozapine for the treatment resistant schizophrenic: a double-blind comparison versus chlorpromazine/benzotropine. *Archives of General Psychiatry*, 45, 789-796.
- Keck, P.E. Jr, Wilson, D.R., Strakowski, S.M., et al (1995) Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. *Journal of Clinical Psychiatry*, 56, 466-470.
- Kee, K.S., Kern, R.S., Marshall, B.D.Jr & Green, M.F. (1998) Risperidone versus haloperidol for perception of emotion in treatment-resistant schizophrenia: preliminary findings. *Schizophrenia Research*, 31, 159-165.
- Kinon, B.J., Kane, J.M. & John, C. (1993) Treatment of neuroleptic resistant schizophrenia relapse. *Psychopharmacology Bulletin*, 29, 309-314.
- Klein, D.F. & Davis, J.M. (1968) *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore, Md: Williams & Wilkins.
- Klieser, E., Lehmann, E., Kinzler, E., et al (1995) Randomised, double-blind, controlled trial of risperidone versus Clozapine in patients with chronic schizophrenia. *Journal of Clinical Psychopharmacology*, 152, 179-82.
- Kulhara P. (1998) Management of schizophrenia: an update. *Indian Journal of Psychiatry*, 40, 120-134.
- Lacey, R.L., Preskorn, S.H. & Jerkovich, G.S. (1995) Is risperidone a substitute for Clozapine for patients who do not respond to neuroleptics?

- (Letter to Editor) *American Journal of Psychiatry*, 152, 1401.
- Leff, J.P., Berkowitiz, R., Shavit, N., et al (1990) A trial of family therapy versus a relatives' group for schizophrenia: a two year follow-up. *British Journal of Psychiatry*, 157, 571-577.
- Leff, J.P., Berkowitiz, R., Shavit, N., et al. (1989) A trial of family therapy vs. a relatives' group for schizophrenia. *British Journal of Psychiatry*, 154, 58-66.
- Lerner, V., Chudakova, B., Kravets, S. & Polyakova, I. (2000) Combined use of risperidone and olanzapine in the treatment of patients with resistant schizophrenia : a preliminary case series report. *Clinical Neuropharmacology*, 23, 284-286.
- Leucht, S., Mcgrath, J., White P. & Kisling, W. (2002) Carbamazepine augmentation for schizophrenia: how good is the evidence? *Journal of Clinical Psychiatry*, 63, 218-224.
- Levinson, D.F., Simpson, G.M. & Sigh, H. (1990) Fluphenazine dose, clinical response, and extrapyramidal symptoms during acute treatment. *Archives of General Psychiatry*, 47, 761-168.
- Lieberman, J.A., Safferman, A., Pollack, S. et al (1994) Clinical effects of Clozapine in chronic schizophrenia: Response to treatment and predictors of outcome. *American Journal of Psychiatry*, 151,1744-1752.
- Lieberman, J.A., Jody, D. & Geisler, S. (1993) Time course and biologic correlates of treatment response in first episode schizophrenia. *Archives of General Psychiatry*, 50, 369-376.
- Lingiaerde, O., Engstrand, E., Ellingsen, P., et al. (1979) Antipsychotic effect of diazepam when given in addition to neuroleptics in chronic psychotic patients: A double-blind clinical trial. *Current Therapy and Research Experiment*, 26, 505-514.
- Marder, S.R. (1996) Management of treatment-resistant patients with schizophrenia. *Journal of Clinical Psychiatry*, 57(Suppl 11), 26-30.
- Martin, J., Gomez, J.C., Garcia-Bernardo, E., et al. (1997) Olanzapine in treatment-refractory schizophrenia: results of an open-label study. The Spanish Group for the Study of Olanzapine in Treatment-Refractory Schizophrenia. *Journal of Clinical Psychiatry*, 58(11), 479-483.
- Mauri, M.C., Volonteri, L.S., Dell'Osso, B., et al. (2003) Predictors of clinical outcome in schizophrenic patients responding to clozapine. *Journal of Clinical Psychopharmacology*, 23, 660-664.
- May, P.R., Dencker, S.J. & Hubbard, J.W. (1988) A systemic approach to treatment resistance in schizophrenic disorders. In Dencker, S.J., ed. *Treatment resistance in schizophrenia*. Braunschweig: Vieweg, pp22-33.
- McEvoy, J.P., Hogarty, G. & Steingard, S. (1991) Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher neuroleptic dose. *Archives of General Psychiatry*, 48, 739-745.
- McFarlen, W.R., Lukens, E., Link, B., et al (1995) Multiple-family groups and psychoeducation in the treatment of schizophrenia. *Archives of General Psychiatry*, 52, 679-687.
- McGlashan, T.H. (1988) A selective review of recent North American long-term follow-up studies of schizophrenia. *Schizophrenia Bulletin*, 14, 515-542.
- Meltzer, H.Y., Lee, M. and Cola, P. (1998) The evolution of treatment resistance: biological implications. *Journal of Clinical Psychopharmacology*, 18, 5S-11S.
- Meltzer, H.Y. (1994) An overview of the mechanism of action of Clozapine. *Journal of Clinical Psychiatry*, 55(Suppl B), 47-52.
- Meltzer, H.Y. (1990) Defining treatment refractoriness in schizophrenia. *Schizophrenia Bulletin*, 16, 563-565.
- Miller, A.L., Chiles, J.A., Chiles, J.K., et al (1999) The TMAP Schizophrenia Algorithms. *Journal of Clinical Psychiatry*, 60, 649-657.
- Miller, R. & Chouinard, G. (1993) Loss of striated cholinergic neurons as a basis of tardive a L-Dopa-Induced dyskinesias, neuroleptic induced supersensitivity psychosis and refractory schizophrenia. *Biological Psychiatry*, 34, 713-738.
- Molina, V., Reig, S., Sarraamea, F., Sanz, J., et al (2003) Anatomical and functional brain variables associated with clozapine response in treatment-resistant schizophrenia. *Psychiatry Research*, 124, 153-161.
- Moncrieff, J. (2003) Clozapine vs conventional antipsychotic drugs for treatment — resistant schizophrenia: a re-examination. *British Journal of Psychiatry*, 183, 161-166.
- Mowerman, S. & Siris, S.G. (1996) Adjunctive loxapine in a clozapine-resistant cohort of schizophrenic patients. *Annals of Clinical Psychiatry*, 8, 193-197.
- Muijen, M., Marks, I.M., Connolly, J., et al (1992) The Daily Living Programme: preliminary comparison of community versus hospital-based treatment for the seriously mentally ill facing emergency admission. *British Journal of Psychiatry*, 160, 379-384.
- Murray, R.M., O' Callaghan, E., Castle, D.J. & Lewis, S. W. (1992) A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin*, 18, 319-332.
- Overall, J.E. & Gorham, D.E. (1961) The brief psychiatric rating scale. *Psychology Report*, 10, 799-812.
- Pato, C.N., Wolkowitz, O.M., Rappor, M. et al (1989) Benzodiazepine augmentation of neuroleptic treatment in patients with schizophrenia. *Schizophrenia Bulletin*, 25, 263-266.
- Peuskens, J. (1999) The evolving definition of treatment resistance. *Journal of Clinical Psychiatry*, 60 (Suppl 12), 4-8.
- Quitkin, F., Rifkin, A. & Klein, D. (1975) Very high dosage vs standard dosage fluphenazine: a double-blind study of non-chronic treatment refractory patients. *Archives of General Psychiatry*, 32, 1276-1281.
- Raskin, S., Katz, G., Zislin, J. et al (2000) Clozapine and risperidone: combination/augmentation treatment of refractory scizophrenia: a preliminary observation. *Acta Psychiatrica Scandinavia*, 101, 334-336.
- Revicki, D.A., Luce, B.R., Weschler, J.M., et al (1990) Cost-effectiveness of Clozapine for treatment resistant schizophrenic patients. *Hospital and Community Psychiatry*, 41, 850-854.
- Rodriguez, V.M., Catalina, M.L., Garcia-Noblejas, J.A. & Cuesta, P. (1998) Schizophrenic syndromes and clozapine response in treatment-resistant schizophrenia. *Psychiatry Research*, 77, 21-28.
- Rosberg, J. & Stunden, R.J. (1990) The use of direct confrontation: the treatment resistant schizophrenic patients. *Acta Psychiatrica Scandanavia*, 81, 352-358.
- Ruskin, P., Averbukh, I., Belmaker, R.H. & Desberg, H. (1979) Benzodiazepine in chronic schizophrenia. *Biological Psychiatry*, 14, 557-558.
- Sajatovic, M. & Meltzer, H.Y. (1993) The effect of short-term electroconvulsive treatment plus neuroleptics in treatment-resistant schizophrenia and schizoaffective disorder. *Convulsion Therapy*, 9, 167-175.
- Sanders, R.D. & Mossman, D. (1999) An open trial of Olanzapine in patients with treatment-refractory psychoses. *Journal of Clinical Psychopharmacology*, 19, 62-66.
- Schatzberg, A.F., Cole, J.O. & Debatista, C. (2003) Augmentation strategies for treatment-resistant disorders. In *Manual of Clinical Psychopharmacology*, Washington, DC: American Psychiatric Press, pp437-480.
- Schooler, N.R., Keith, S.J., Severe, J.B., et al (1997) Relapse and rehospitalization during maintenance treatment of schizophrenia. *Archives of General Psychiatry*, 54, 453-460.
- Schulz, S.C., Thompson, P.A., Jacobs, M., et al (1999) Lithium augmentation fails to reduce symptoms in poorly responsive schizophrenic outpatients. *Journal of Clinical Psychiatry*, 60, 366-372.
- Schulz, S.C., Kahn, E.M., Baker, R.W. & Conely, R.R. (1990) Lithium and carbamazepine augmentation in treatment-refractory schizophrenia. In: Angrist B., Schulz S.C. (ed) *The Neuroleptic nonresponsive patient: Characterization and Treatment* Washington, DC: American Psychiatric Press, pp: 109- 136.
- Seeley, W.W., Turetsky, N., Reus VI & Wolkowitz, O.M. (2002) Benzodiazepines in schizophrenia: prefrontal cortex atrophy predicts response to alprazolam augmentation. *World Journal of Biological Psychiatry*, 3, 221-224.
- Shalev, A., Hermesh, H. & Rothberg, J. (1993) Poor neuroleptic response

in acutely exacerbated schizophrenic patients. *Acta Psychiatrica Scandinavica*, 87, 86-91.

Shiloh, R., Zemishlany, Z., Aizenberg, D., et al (1997) Sulpiride augmentation in people with schizophrenia partially responsive to Clozapine: A double-blind, placebo-controlled study. *British Journal of Psychiatry*, 171, 569-573.

Shore, D. (1995) Clinical implications of clozapine discontinuation. Report of an NIMH workshop. *Schizophrenia Bulletin*, 21, 333-338.

Small, J.G., Klapper, M.H., Malloy, F.W. & Steadman, T.M. (2003) Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. *Journal of Clinical Psychopharmacology*, 23, 223-228.

Small, J.G., Kallams, J.J., Milstein, V., & Moore, J.A. (1975) A placebo-controlled study of lithium combined with neuroleptics in chronic schizophrenic patients. *American Journal of Psychiatry*, 132, 1315-1317.

Smith, T.E. & Docherty, J.P. (1998) Standards of care and clinical algorithms for treating schizophrenia. *Psychiatric Clinic of North America*, 21, 203-220.

Stahl, S.M. (1999) Antipsychotic polypharmacy, Part-I: Therapeutic option or dirty little secret? *Journal of Clinical Psychiatry*, 60, 425-426.

Tarrier, N., Barrowclough, C., Proveddu, K. & Fitzpartick, E. (1994) The Salford Family Intervention Project: relapse rates of schizophrenia at five and eight years. *British Journal of Psychiatry*, 165, 829-832.

Tarrier, N., Lowson, K. & Barrowclough, C. (1991) Some aspects of family interventions in schizophrenia. II: Financial considerations. *British Journal of Psychiatry*, 159, 481-484.

Tarrier, N., Barrowclough, C., Vaughn, C.E., et al. (1989) Community management of schizophrenia in a two year follow-up of a behavioural intervention with families. *British Journal of Psychiatry*, 154, 625-628.

Tarrier, N., Barrowclough, C., Vaughn, C.E., et al (1988) The community management of schizophrenia: a controlled trial of a behavioural intervention with families to reduce relapse. *British Journal of Psychiatry*, 153, 532-542.

Taylor, C.G., Flynn, S.W., Altman, S. et al. (2001) An open trial of risperidone augmentation of partial response to clozapine. *Schizophrenia*

Research, 48,155-158.

Telles, C., Karno, M., Mintz, J., et al (1995) Immigrant families coping with schizophrenia. Behavioural family intervention vs. case management with low income Spanish-speaking population. *British Journal of Psychiatry*, 167, 473-479.

Terkelsen, K.G. & Grosser, R.C. (1990) Estimating clozapine's cost to the nation. *Hospital and Community Psychiatry*, 41, 863-869.

Tharyan, P. (2000) Electroconvulsive therapy for schizophrenia. *Cochrane Database Systemic Review*, 2, CD0:00076.

Thomas, S.G. & Labbate, L.A. (1998) Management of treatment-resistant schizophrenia with olanzapine. *Canadian Journal of Psychiatry*, 43, 195-196.

Torrey, E.F. (1986) Management of chronic schizophrenic outpatients. *Psychiatric Clinic of North America*, 9, 143-148.

Van Putten, T., Marder, S.R. & Mintz, J. (1990) A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. *Archives of General Psychiatry*, 47, 754-758.

Wassef, A., Dott, S.G., Harris, A., et al (2000) Randomised, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *Journal of Clinical Psychopharmacology*, 20, 357-361.

Weinberger, D.R. (1995) Schizophrenia: from neuropathology to neurodevelopment. *Lancet*, 346, 552-557.

Wirshing, D.A., Marshall, B.D. Jr, Green, M.F., et al (1999) Risperidone in treatment-refractory schizophrenia. *American Journal of Psychiatry*, 156, 1374-1379.

Wolkowitz, O.M., Turetsky, N., Reus, V.I. & Hargreaves, W.A. (1992) Benzodiazepine augmentation of neuroleptics in treatment-resistant schizophrenia. *Psychopharmacology Bulletin*, 28, 291-295.

Wyatt, R.J. (1991) Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, 17, 235-242.

Wykes, T. & Carson, J. (1996) Psychosocial factors in schizophrenia: implications for rehabilitation and community care. *Current Opinion in Psychiatry*, 9, 68-72.