INTRODUCTION

Schizophrenia is one of the major mental health problems of our time. It is prevalent worldwide and rates of 2-3 per 1000 reported from India (Murthy et al., 1997) are in line with other countries. The illness has substantial short-term and long-term consequences for the individuals affected, their families, and the society. The symptoms can cause immense distress to patients, and are often associated with a variety of social and occupational impairments. There is also an increased incidence of several medical disorders and mortality, especially from suicide. The condition usually disrupts the family life of afflicted persons, and has considerable adverse impact on relatives or caregivers. The social and economic burden it poses for the community makes it one of the most serious health problems faced by the society.

Cross-cultural studies have shown that culture has an important effect on the natural history of the disorder. (Jablensky et al., 1992; WHO, 1973) The socio-cultural milieu of developing countries like India seem to augur for a more favourable course and outcome, though the reasons for this are not quite clear. Over the years there have been many new advances in the understanding and management of schizophrenia. Not surprisingly, these developments have had a positive impact on the way the condition is managed in India. Despite this the lot of a majority of the Indian patients does not seem to have improved. This is partly because the lack of sustained efforts to adapt existing treatments to suit the specific requirements of Indian patients and their families. Part of the difficulty also lies in the mental health services presently existing in the country. Treatment facilities vary widely but a shortage of trained personnel and sparse community resources are common to all. Lack of awareness about mental illness, stigma encountered by sufferers and their kin, belief in supernatural causation and traditional methods of care often compound these problems. Poverty, lack of education, and inadequate access to health care facilities also place severe constraints on what can be offered. In this situation simple replication of Western treatment models and strategies is clearly neither possible, nor appropriate. The need to develop treatments tailored to meet the requirements of our patients and appropriately match the existing resources has been voiced time and again. However, very little has been achieved.

The current document is a small step towards meeting this need by formulating certain principles to guide the treatment of schizophrenia in the Indian context. The aim is to set down certain minimum standards that need to be taken into account while caring for our patients and their families.

SCOPE OF THIS DOCUMENT

These guidelines seek to summarize data available on major treatments available for people with schizophrenia, with the hope that this knowledge will help ensure uniform standards of care. They are neither comprehensive nor definitive. Psychiatrists caring for a patient should consider, but not be limited to the recommendations made. Patients of schizophrenia are cared for in a number of different settings in our country. In their present form these guidelines are particularly applicable to general hospital psychiatric units on the assumption that such units cater to a majority of these patients.
These might not be wholly suitable for other treatment settings. They are also meant principally for adult patients. Finally, they must be regarded only as a preliminary effort, especially given the paucity of previous work in this area in India. It is expected that several modifications and revisions will be required to improve their usefulness. Inputs from all mental health professionals in the country in this regard will thus be more than welcome.

GUIDELINES REVIEWED
5. Texas Medication Algorithm Project (TMAP). Schizophrenia algorithms (Miller et al., 1999).
8. The Royal College of Psychiatrists' consensus statement on the use of high-dose antipsychotic medication (Thompson 1994).

REVIEW OF TREATMENT MODALITIES

GENERAL ISSUES
Consideration has to be given to several factors while treating a patient with schizophrenia. Among others these would include clinical issues (both cross-sectional and longitudinal), socio-cultural variables such as attitudes to and beliefs about the illness or its treatment, service parameters e.g. the type of treatment facilities available, and so on. Despite considerable differences in such factors for individual patients, certain elements of care are common to all. Many patients with the condition will require comprehensive and continuous treatment for prolonged periods. Wherever possible an integrated, biopsychosocial approach to care will need to be adopted. An active collaboration with the family while planning and delivering treatment is almost always required. Management should be sensitive to the patient's needs and empirically titrated to the patient's response and progress.

Since there is no cure for the condition, treatment seeks to decrease the morbidity and mortality associated with the disorder. The general goals of treatment are to decrease the frequency, severity and consequences of episodes (exacerbations) and maximize functioning between episodes. Specific goals depend on the specific phases of illness.

IMPORTANT CONSIDERATIONS IN TREATMENT
• Comprehensive and continuous treatment for prolonged periods for most
• Integrated, bio-psychosocial approach to care
• Active collaboration with the family while planning and delivering treatment
• Treatment sensitive to the patient's needs and empirically titrated to the patient's response and progress.

PHASES OF ILLNESS/TREATMENT

Acute phase

This is the florid psychotic phase during which patients exhibit symptoms such as delusions or hallucinations, disorganized thinking, behavioural disturbances e.g. extreme agitation or retardation etc. Their functioning is severely impaired, they are unable to care for themselves, and can be at risk of harming themselves or others. The principal tasks of treatment are reduction of symptoms and risk of harm, and improvement of functioning. (APA, 1997; NICE, 2002; CRAG/SCOTMEG, 1995).

POST-ACUTE PHASE/STABILIZATION PHASE/CONTINUATION-TREATMENT PHASE

This phase begins once the acute symptoms reduce in severity or remit. Consolidation of remission, continued reduction in symptoms and prevention of early relapses are the usual treatment objectives during this phase, which lasts about 6 months (APA, 1997; NICE, 2002).

STABLE PHASE/Maintenance Treatment Phase

Symptoms are stable and usually less severe than in the acute stage. Negative symptoms may predominate and deficits in social and occupational functioning become more apparent. Maintaining or improving level of functioning and prevention of recurrences are the major aims of treatment (APA, 1997; NICE, 2002; Saito & Saijo, 1999).

TREATMENT-PHASES AND GOALS

ACUTE PHASE
• Reduction of symptoms and risk of harm, improvement of functioning

POST-ACUTE PHASE
• Consolidation of remission, continued reduction in symptoms, prevention of early relapses

STABLE PHASE
• Maintaining/improving level of functioning, prevention of recurrences

BASIC INGREDIENTS OF TREATMENT

Whatever be the phase of illness, goals of treatment, or social and cultural circumstances, certain basic principles of treatment are applicable to most, if not all patients. These include:

1. Comprehensive assessment - A systematic and comprehensive assessment of the patient's problems, which include an evaluation of psychiatric, physical, psychosocial and cultural aspects, is the essential first step of implementing treatment. Assessments and reassessments have to be continuous and ongoing.

2. Evolving a treatment plan / regular updating - Every patient should have a well thought out treatment plan which should preferably be documented. This plan should be prepared in consultation with, and be agreed upon by relatives/carers, the patient (whenever appropriate) and other professionals involved in treatment. Since needs of patients are likely to vary with time, this plan will need to be revised and updated regularly depending on the demands of the situation.

3. Monitoring - Continuous monitoring of clinical status, response to treatment, adverse effects etc. is necessary to pre-empt relapses and prevent setbacks.

4. Forming a therapeutic alliance - A supportive therapeutic alliance with the patient forms the
foundation on which treatment is carried out. Mutual trust, respect and continuity of care greatly aid this process.

5. Collaborating with the family - A similar alliance with the family also furthers treatment. Relatives are invaluable sources of information; they can help by endorsing treatment decisions, ensuring compliance with treatment, closely monitoring the patient's condition and providing support for the patient. To enable them to act effectively in this role they need to be involved, educated, as well as helped and supported themselves.

6. Ensuring adherence to treatment - A large percentage of patients do not comply with treatment or drop out at various stages. Their reasons for doing so may vary from mistaken beliefs to the experiencing of unpleasant side effects. Being aware of the phenomenon of non-adherence, creating an atmosphere where such problems can be freely discussed by patients, being sensitive to their needs, and modifying treatment to deal with such situations can often help in minimizing non-compliance and its consequences.

PHARMACOLOGICAL TREATMENT

Medications are used for the treatment of acute episodes, prevention of relapses and recurrences, and improvement of symptoms in the interim. Antipsychotic agents are the mainstay of treatment with antidepressants, mood stabilizers or benzodiazepines being useful adjuncts.

ANTIPSYCHOTICS

The modern era of drug treatment of psychotic disorders began with the discovery of antipsychotic properties of chlorpromazine in the early 1950s. Till about the 1990s conventional antipsychotics of this kind were the only drugs available for treatment of schizophrenia. Though highly effective these drugs have several limitations. They cause acute and chronic extrapyramidal side effects (EPSEs), some of which can be serious or irreversible. They do not alleviate all symptoms of schizophrenia, are partially effective in a substantial proportion of patients, and largely ineffective for some signs and symptoms. NICE, 2002; Marder & van Kammen, 2000; van Kammen & Marder, 2000). These deficiencies were sought to be overcome with the introduction of a newer group of agents such as clozapine, risperidone and olanzapine. These drugs appear to have a better risk/benefit ratio and several other advantages. Then again, much of the claims regarding their usefulness are still under scrutiny (Sartorius et al., 2002; 2003; van Kammen & Marder, 2000).

TERMINOLOGY

Drugs useful in treatment of psychosis have been referred to as neuroleptics or major tranquillisers, but the term antipsychotic is considered more appropriate. Similarly, the older group goes by the name of traditional, conventional or typical antipsychotics. The more acceptable term, however, is first-generation antipsychotic medications (FGAMs), as opposed to second-generation antipsychotic medications (SGAMs), a term that refers to drugs such as clozapine, risperidone, olanzapine etc (Sartorius et al., 2002; 2003; Lohr & Braf, 2003).

FIRST-GENERATION ANTIPSYCHOTIC MEDICATIONS

TYPES

Members include agents from diverse pharmacological groups such as phenothiazines (chlorpromazine, thioridazine, trifluoperazine, fluphenazine etc.), butyrophenones (haloperidol, droperidol, trifluoperidol etc.), thioanxethenes (thiothixene, zuclopenthixol, flupenthixol etc.), diphenylbutylpiperidines (pimozide, penfluridol etc.), dihydronindolones (molindone), dibenzoxazepines (loxapine), substituted benzamides (sulpiride) and other drugs e.g. oxypertine. The therapeutic response to these drugs is thought to be related to their ability to block D2 receptors. FGAMs are also traditionally divided into high potency drugs (classically haloperidol), which have higher likelihood of causing EPSEs. Low potency agents (typically chlorpromazine) have greater propensity to cause anticholinergic
and cardiovascular side effects (APA, 1997; NICE, 2002; van Kammen & Marder, 2000).

Efficacy

Acute Phase

Randomised controlled trials/systematic reviews/meta-analyses - The evidence for acute phase efficacy of FGAMs comes from numerous double-blind randomised controlled trials (RCTs), starting with studies from the National Institute of Mental Health, U.S.A. (NIMH Psychopharmacology Service Centre Collaborative Study Group, 1964) and replicated by several other researchers. In addition there are several reviews and meta-analytic studies of their effectiveness. All these trials have provided compelling evidence for the efficacy of these drugs in every subtype and subgroup of schizophrenia (Marder & van Kammen, 2000; Klein & Davis, 1969; Janiacak et al., 1993; Lehman et al., 1998).

Although these drugs are effective in diminishing most symptoms of schizophrenia, their effect is most marked on positive symptoms. Early appraisals of the usefulness of these drugs noted that approximately 60% of patients treated for 6 weeks achieve complete, or near complete remission, 40% have moderate to severe symptoms, while 8% do not improve at all. A more recent review confirmed the efficacy of these drugs in reducing positive symptoms during acute psychotic episodes with remissions of positive symptoms being achieved in 70% of the cases. Efficacy is relatively less in case of other symptom-groups e.g. negative symptoms or disorganization, but even these symptoms improve to some degree. However, response patterns are complex and complicated by the frequent emergence of side effects such as EPSEs. All FGAMs are equally effective, and the proposal that low potency agents are more effective for agitated, and high potency agents for withdrawn patients, has never been substantiated by controlled trials. As a group, female patients respond better and require smaller doses, but the only reliable predictor of response is the patient's prior response (Marder & van Kammen, 2000; NIMH Psychopharmacology Service Centre Collaborative Study Group, 1964; Klein & Davis, 1969; Janiacak et al., 1993; Lehman et al., 1998).

Maintenance Phase

A large number of RCTs, reviews and some meta-analytic studies have also consistently documented the usefulness of FGAMs in prevention of relapses. Many more patients (53%-75%) who come off drugs or are switched to placebo tend to relapse, than those who continue with their medication (16%-24%) (Marder & van Kammen, 2000; Davis, 1975; Hogarty, 1976; Kane, 1990; Davis et al., 1993).

Maintenance medication is also useful in preventing relapse among first-episode patients, although relapse rates tend to be lower in this population.

Other studies have found that patients who relapsed while on drugs had less severe episodes with less likelihood of violence, self-harm and antisocial acts. Patients not taking treatment were more likely to be admitted involuntarily, and ended up requiring a higher total dose of medication.

Nevertheless, maintenance treatment with FGAMs has its limitations. Many patients become non-compliant, and relapse rates are still very high in those who carry on with their drug-treatment. There are often considerable socio-occupational deficits in those who respond, and adverse outcomes such as permanent institutionalisation or suicide are not uncommon (Marder & van Kammen, 2000).

Side Effects

Sedation

Sedation is the single most common side effect of these drugs. It is more common with low potency agents. It is more evident during the initial phases, but some tolerance develops with continued treatment. Sedation can be beneficial for agitated patients; however, daytime drowsiness often causes problems. In such situations reducing doses, administering medication as a single bedtime dose, or
switching to a less sedating drug can be helpful (APA, 1997; Marder & van Kammen, 2000; Arana, 2000).

ANTICHOLINERGIC EFFECTS

These include problems such as constipation, dry mouth, blurred vision, urinary retention, tachycardia etc. They occur in about 10%-50% of treated patients, and are more common with low potency agents. Such adverse effects are usually mild but can occasionally lead to serious complications like paralytic ileus. Elderly patients, those with prostatic hypertrophy, or narrow-angle glaucoma are particularly at risk. The more rare syndrome of central anticholinergic toxicity can impair cognitive functions, or even lead to delirium. It normally occurs in those taking drugs with high anticholinergic activity (e.g. chlorpromazine or thioridazine), along with antiparkinsonian medication, in the elderly, debilitated or the physically ill. Cessation of drugs usually leads to complete reversal of symptoms, although parenteral phystostigmine may occasionally be required (APA, 1997; Marder & van Kammen, 2000; Arana, 2000).

POSTURAL HYPOTENSION

This is due to antiadrenergic effects of FGAMs and commoner among low potency agents. Patients usually complain of mild giddiness while getting up. It can lead to falls especially in the elderly with serious consequences such as fractured hips. More severe hypotension can cause syncopal episodes. Patients are advised to be careful while getting up, increase salt and fluid intake and use elastic stockings. Corticosteroids such as fludrocortisone may need to be used in very severe cases of hypotension (APA, 1997; Marder & van Kammen, 2000; Arana, 2000).

NEUROLOGICAL SIDE EFFECTS

EXTRA PYRAMIDAL SIDE EFFECTS (EPSES)

Up to 60% of patients on treatment with first-generation drugs, particularly those on high potency agents such as haloperidol can develop EPSEs. From the patient’s perspective EPSEs are often more distressing than the symptoms of the disorder and a major cause of non-compliance. EPSEs can be acute with onset within days to weeks of starting treatment; these are dose dependent and usually reversible. Chronic EPSEs occur after months or years of treatment, are not clearly dose dependent, and can persist even after the offending drugs have been withdrawn (APA, 1997; Marder & van Kammen, 2000; Arana, 2000).

ACUTE EPSES

DYSTONIA

Acute dystonias occur in about 10% of those starting treatment. Onset is often after the first few doses and 90% of the dystonic reactions occur within 3 days of treatment. Young men, on high doses of high potency medication and intramuscular preparations are particularly at risk. Symptoms include intermittent, sustained spasms of discrete muscle groups of head, neck and trunk. Dystonias appear quite suddenly, are very frightening for the patient, and in some situations (e.g. laryngeal dystonias) even life threatening. They respond very well to parenteral administration of anticholinergics, benzodiazepines or antihistamines. Recurrences can be prevented by administration of oral anticholinergics (APA, 1997; Marder & van Kammen, 2000; Arana, 2000; King, 1995).

MEDICATION-INDUCED PARKINSONISM

This side effect is found in 20%-30% of patients receiving treatment. Onset is within the fist few days to weeks of treatment and is dose dependent. Symptoms resolve on drug withdrawal, but can occasionally persist, especially in the elderly. Risk factors include old age, female sex, a prior history of similar symptoms, and basal ganglia disease. Clinical features include bradykinesia, rigidity and tremor. A milder form (akinesia) occurs in about half of the treated patients and is associated with
depressive symptoms (akinetic depression) and cognitive impairment. It is often difficult to distinguish from negative symptoms.

Parkinsonian symptoms can be effectively treated with anticholinergic/antiparkinsonian medications such as trihexyphenidyl, procyclidine, orphenadrine, benzhexol, benztropine and biperiden, but these should be used cautiously. Antihistaminics (diphenhydramine) and amantadine are useful second line alternatives. Symptoms also respond to reductions in antipsychotic dose (when this is possible), or on changing to an alternative drug, preferably a second-generation one (APA, 1997; Marder & van Kammen, 2000; Arana, 2000; King, 1995).

AKATHISIA

Akathisia is a peculiar state of somatic restlessness manifesting both subjectively and objectively in about 25%-50% patients on antipsychotics. Patients complain of inability to sit still and are commonly seen fidgeting or pacing. It usually appears by the fifth day of treatment or earlier. It is one of the most distressing and difficult to treat side effect. It is associated with poor outcome and suicide attempts. Chronic and tardive forms have also been reported. Akathisia is commoner among women, in patients on high doses of mostly (but not always) high potency drugs.

Beta-blockers such as propranolol are the most established form of treatment. Benzodiazipines are also helpful, but not anticholinergic drugs unless there is coexisting Parkinsonism (APA, 1997; Marder & van Kammen, 2000; Arana, 2000; King, 1995). More recently, serotonin (5HT2a) antagonists such as mianserin, ritanserin and cyproheptidane have been found to be efficacious in the treatment of akathisia (Poyurovsky et al., 2001). Reducing the dose of the antipsychotic or switching to a second-generation drug are reasonable alternatives.

THE ROLE OF PROPHYLACTIC ANTICHOLINERGIC TREATMENT

The role of prophylactic anticholinergic medication is still controversial. Some studies have shown the benefit of this approach in lowering the rates of EPSs, particularly acute dystonias. However, tolerance usually develops to EPSs and anticholinergics are unnecessary after 3-6 months in all but 10% of patients (King, 1995). Moreover, anticholinergics have troublesome side effects of their own, can interact adversely with antipsychotics, can be abused, and have the potential to precipitate tardive dyskinesia. These considerations led a WHO statement on this issue to recommend against prophylaxis (WHO, 1990). However others believe that prophylactic treatment is necessary when there is a high risk of EPSs (e.g. young men on high potency agents), a predisposition to EPSs (e.g. a prior history), or likely detrimental consequences of EPSs, e.g. non-compliance (Casey & Keepers, 1985).

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

This is a rare (prevalence 1%-2%), but potentially fatal adverse effect of antipsychotic treatment. It is characterized by severe rigidity, hyperthermia, clouding of consciousness and autonomic instability such as hypertension or tachycardia. Elevations of creatinine phosphokinase and liver transaminases, leukocytosis, myoglobinemia and myoglobinuria are also reported. Mortality rates are high, up to 20%, though with recent improvements in detection and management these rates are likely to have fallen.

NMS is commoner among young males on high doses of high potency medications, particularly parenteral forms, who have had rapid escalation of their doses. Haloperidol is often the culprit, and combinations with lithium are particularly neurotoxic. Physical illness, neurological disability and dehydration are the other risk factors.

Early detection, immediate discontinuation of antipsychotics, prompt institution of supportive treatment measures and intensive monitoring are the principal steps of management. Drugs such as dantrolene, bromocriptine or amantadine can accelerate the reversal of the process and should always
be tried. After several weeks of recovery antipsychotics can be cautiously resumed with a lower potency drug (APA, 1997; Marder & van Kammen, 2000; Arana, 2000; King, 1995).

**ACUTE/PARADOXICAL DYSKINESIAS**

Acute onset dyskinetic movements resembling tardive dyskinesia may also occur with antipsychotic treatment. These respond well to anticholinergic medication (King, 1995; Casey & Keepers, 1985).

**CHRONIC EPSES**

**TARDIVE DYSKINESIA**

Tardive dyskinesia (TD) is an involuntary movement disorder that follows long-term treatment with antipsychotics. The mean reported prevalence is 15%-20% worldwide, with an annual incidence of 4%-5% in the first few years of treatment. The classical picture is one of orofacial and bucco-lingual movements, but a range of other movements such as choreoathetoid movements of limbs, tics, abnormal postures, hemiballismus, grunting vocalizations and disturbances of respiration can also occur. Risk factors include old age, female gender coupled with postmenopausal status, diagnosis of affective disorder (especially major depression), concurrent physical disorders such as diabetes, higher doses of medication and longer durations of treatment, prior history of EPSEs, alcohol abuse etc. In most patients, particularly the young and those with recent onset TD, the disorder is mild and non-progressive. TD might become irreversible if antipsychotics are continued, but even in these cases some improvement does occur. If drugs are stopped the outcome is better.

TD can be prevented to a great extent by using minimum effective doses of antipsychotics during long-term treatment, by regular monitoring and early detection. When TD is suspected other potential causes of dystonias (e.g. Huntington’s or Wilson’s disease) need to be ruled out. Discontinuation of the antipsychotic may be considered, but only in stable and remitted patients. Gradual dose reduction is the other alternative. These manoeuvres might lead to a temporary worsening of movements (withdrawal dyskinesias), which usually diminish with time. If reduction in dose is not possible because of the risk of relapse, a trial of Vitamin E (1600 IU/day) is recommended by some authors. The more common advice, however, is to switch to a second-generation agent which have lower propensity to cause TD. The final option is to treat with clozapine. Though there are very few RCTs of treatment of TD with clozapine, the available evidence indicates that some patients benefit from this drug (APA, 1997; Marder & van Kammen, 2000; Arana, 2000; King, 1995; Glazer, 2000; Simpson, 2000).

**PERIORALTREMOR (RABBIT SYNDROME)**

A rapid perioral tremor which can occur at any point during antipsychotic treatment, but which usually arises after several months, has been occasionally reported. The tremor responds well to anticholinergics (Marder & van Kammen, 2000; Casey & Keepers, 1985).

**CARDIOVASCULAR EFFECTS**

Low potency agents such as chlorpromazine or thioridazine can cause ECG abnormalities such as prolongation of PR and QTc intervals, T-wave blunting or inversion, and ST segment depression. Malignant arrhythmias such as torsae de pointes that are potentially lethal have also been reported (APA, 1997; Marder & van Kammen, 2000; Arana, 2000).

There is now increasing awareness of the risk of sudden deaths with antipsychotics. Although a causal link is as yet unclear, studies suggest that the association with thioridazine is particularly strong. Unexpected deaths have also occurred in a number of young patients without pre-existing cardiac disease who have been treated with high doses of pimozide (Thompson, 1994). A recent review of this area concluded that although, pimozide, sertindole, droperidol and haloperidol have been documented to cause torsae de pointes and sudden death, the most marked risk was with thioridazine (Glassman et al., 2001). Another naturalistic study also found prolonged QTc intervals
were strongly associated with thioridazine and droperidol (Reilly et al., 2002). Following this, restrictions have been placed on the use of thioridazine and pimozide, and droperidol has been withdrawn. Then again similar side effects have been reported with a number of other antipsychotics. Indeed, some authors feel that until further evidence is available it will be prudent to assume that all antipsychotics have the potential to increase the risk of serious arrhythmias and cause sudden death (Ray, & Meador, 2002). Sudden deaths could also result from drug-induced seizures, hypotension, asphyxiation, aspiration, paralytic ileus, hyperthermia, NMS etc. Old age, pre-existing disease, dehydration, stress, agitation and exhaustion are the potential risk factors. Proper screening, judicious use of antipsychotics, adequate medical and nursing care, and regular monitoring are required to prevent such unfortunate events (APA, 1997; Thompson, 1994). Drugs such as thioridazine should not be used as first line treatments. High doses of pimozide should not be used and regular ECG monitoring is required during treatment (Thompson, 1994).

SEIZURES

All FGAMs can lower seizure threshold and precipitate seizures. The risk is below 1% at conventional dose ranges, those with pre-existing seizure disorders are at higher risk. If a seizure happens, antipsychotic medication should be withdrawn or dose reduced by half till further evaluation is possible (APA, 1997; Marder & van Kammen, 2000).

ENDOCRINE EFFECTS

All first generation drugs block D2 receptors and cause elevation of prolactin levels. Prospective studies have shown that 3-9 weeks of treatment at therapeutic doses increases mean baseline levels of prolactin by up to ten-fold. Hyperprolactinemia is more common in women than men, and women also have significantly greater elevations of prolactin. In them it commonly results in amenorrhoea with or without galactorrhoea; existing data reveal that this may affect 17%-78% of women on long-term antipsychotic treatment. Hyperprolactinemia can also cause breast enlargement, ovarian dysfunction, sexual dysfunctions, premature bone loss and several other adverse effects (Wieck, & Haddad, 2003). Dose reduction helps, but when not feasible addition of low doses of bromocriptine or amantadine is recommended (APA, 1997).

WEIGHT GAIN

Weight gain occurs in about 40% of patients on first generation agents, with all drugs apart from molindone (APA, 1997). Thioridazine seems to be associated with the maximum weight gain although the magnitude of the problem seems to be lesser than some second generation drugs Allison et al., 1999; Allison & Casey, 2001). Weight gain has a number of physical consequences and can also lead to non-compliance. Periodic monitoring and recommendations for changes in diet and exercise can be used to control weight. The role of weight reducing drugs in such situations such as sibutramine, topiramate or orlistat is still not entirely clear (Allison & Casey, 2001; Blackburn, 2000).

SEXUAL DYSFUNCTION

Virtually all FGAMs are associated with sexual problems including ejaculatory disturbances, impotence, decreased libido and changes in quality of orgasm in men, and lowered libido and orgasmic dysfunction in women. The prevalence is about 45%, and thioridazine is again one of the worst culprits (Smith et al., 2002). Dose reductions or discontinuation usually results in improvement or elimination of symptoms. Although adjunctive medications have been used there is still little evidence of their effectiveness (APA, 1997).

CUTANEOUS EFFECTS

These occur infrequently with antipsychotics. Stopping treatment or adding an antihistamine is usually effective (APA, 1997; Marder & van Kammen, 2000).
JAUNDICE

Cholestatic jaundice occurs in less than 0.5% of patients treated with chlorpromazine and requires discontinuation of treatment (APA, 1997; Marder & van Kammen, 2000).

OPHTHALMOLOGIC EFFECTS

Pigmentary retinopathies and corneal opacities are known to occur with low potency agents such as chlorpromazine or thioridazine, at high doses. Routine eye checks can detect these problems. High doses should be avoided (APA, 1997; Marder & van Kammen, 2000).

BLOOD DYSCRASIAS

A benign leucopenia is seen in 10% of patients on treatment with chlorpromazine, agranulocytosis is rare and reported in 0.32% of these patients (APA, 1997; Marder & van Kammen, 2000).

CHOICE OF DRUG/DOSES

Since all FGAMs are equally effective the only guides to choice of a particular drug are past response and side effect profiles. In practice high potency agents are used more often probably because they are comparatively safer, can be increased rapidly, and can be administered parenterally with relative ease (APA, 1997).

Then again, low potency agents have the advantage of being more sedative, an effect that is particularly useful in acutely ill agitated patients. Accordingly, they are preferred by many clinicians (King, 1995).

Although doses have to be titrated for each patient, in general moderate doses (500-900mg/day of chlorpromazine or its equivalent) are better than high (above 800 mg/day) or low doses (less than 250 mg/day) (Marder & van Kammen, 2000; Baldessarini et al., 1988). High doses of medication are neither more effective, nor faster acting. Instead they are associated with a number of side effects, some of which (NMS, sudden death etc.) are potentially lethal. For these reasons a Royal College of Psychiatrists (U.K.) Consensus Panel has expressly recommended against use of high dose medication even in emergency situations, during acute treatment, or for patients resistant to treatment (Thompson, 1994).

DOSING STRATEGIES ARE DIFFERENT FOR THE MAINTENANCE PHASE OF TREATMENT.

ROUTE OF ADMINISTRATION

Tablets are the most common form of administration. Rapidly dissolving formulations or liquid preparations are also available for some drugs. They might be absorbed more rapidly, and could be of some use in patients who spit their tablets out when not observed. Intramuscular (i.m.) or intravenous (i.v.) preparations are faster acting and useful in acute emergencies. Long-acting depot preparations are better at ensuring compliance and are used in maintenance treatment.

INTERACTIONS

There are a number of clinically significant interactions with other psychotropics and central nervous system depressants, antihypertensives, cimetidine, anticonvulsants, chloroquine etc.

BLOOD LEVELS

Earlier studies were unable to find a reliable relation between plasma levels of first-generation drugs and clinical response. More recently such a relationship has been demonstrated for haloperidol in some studies. Even then routine monitoring of plasma levels is not supported by current empirical evidence, except in cases of inexplicable non-response or side effects (Marder & van Kammen, 2000).

SECOND-GENERATION ANTIPSYCHOTIC MEDICATIONS

TYPES

These medications include clozapine, risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole,
sertindole, zotepine and amisulpiride. Most of these drugs have action on serotonin and dopamine receptors, hence are referred to as serotonin-dopamine antagonists (SDAs). However, there is great variability in the pharmacological profile of these agents. For example, amisulpiride is a selective D2/D3 antagonist and aripiprazole has actions on both presynaptic and postsynaptic DA receptors. Clozapine is unique in its actions at multiple receptors, limbic selectivity, and low D2 activity (Sartorius et al., 2002; 2003).

EFFICACY

CLOZAPINE

Although the efficacy of clozapine had been demonstrated earlier, the landmark trial by Kane et al. (1988) proved to be a turning point for this drug. In this 6-week RCT of treatment-refractory patients, those treated with clozapine did substantially better than those with chlorpromazine on a number of measures. Subsequent trials confirmed this efficacy. More recently, the role of clozapine has been examined in other situations such as moderately refractory schizophrenia and first-episode patients. In a 29-week RCT of moderately refractory patients clozapine was found to be superior to haloperidol on various measures such as response rates, number of drop outs, positive symptom efficacy etc. (Kane et al., 2001). Volavka et al. (2002) compared the efficacy of clozapine, olanzapine, risperidone and haloperidol in a 14-week RCT. Clozapine and olanzapine (but not risperidone) were significantly more efficacious than haloperidol, although clinical differences were modest. Several meta-analyses have also been performed to determine the treatment-efficacy of clozapine in schizophrenia. A Cochrane review of comparative RCTs concluded that clozapine was more effective than FGAMs in all types of schizophrenia, but the comparative advantage of clozapine was greater in treatment-resistant patients (Wahlbeck et al., 1999). Results of a meta-analysis by Chakos et al. (2001) also indicated that clozapine was superior to FGAMs, both in terms of efficacy and safety, in patients with treatment-resistance, although the magnitude of treatment effects was not consistently robust. Efficacy data for other SGAMs in treatment-refractory schizophrenia was inconclusive. This notion of clozapine's superiority has, however, been challenged by a recent meta-analysis of 10 trials by Moncrieff (2003) that failed to reveal a substantial advantage for clozapine in terms of a clinically relevant effect, when compared with FGAMs in treatment-refractory patients. The relative effectiveness of clozapine compared to other SGAMs seems to be more uncertain. A Cochrane review on the subject found no difference between the efficacy of clozapine and other SGAMs in patients with treatment-refractory schizophrenia (Tuunainen et al., 2002). Results of another meta-analysis performed for the NICE arrived at similar conclusions; clozapine was consistently superior to FGAMs in treatment-resistant patients in this analysis, but inconsistently so compared to olanzapine and risperidone (NICE, 2002).

RISPERIDONE

The efficacy of risperidone in treatment of chronic schizophrenia was compared with placebo and haloperidol in a number of large multi-centric RCTs employing variable-dose and fixed-dose designs (van Kammen & Marder, 2000; Chouinard et al., 1993; Marder & Meibach, 1994; Peuskens et al., 1995). Risperidone in the doses of 6mg/day or in the dose range of 4-8 mg/day was superior to haloperidol on a number of measures and caused fewer EPSEs. Subsequent trials with first-episode patients have suggested that doses in the range of 2-4 mg/day lead to better outcomes than haloperidol, and no clinically significant EPSEs (Kopala et al., 1997; Emsley et al., 1999). Meta-analytic studies have also concluded that risperidone is superior to placebo, and at least as effective as, or superior to FGAMs such as haloperidol (van Kammen & Marder, 2000). Another meta-analysis of risperidone in treatment of negative symptoms found that risperidone was superior to first-generation agents in this regard as well (Carman et al., 1995). Finally, at least 2 RCTs have shown risperidone to be better than haloperidol in patients with treatment-refractory schizophrenia (Bondolfi et al., 1998; Wirshing et al., 1999).
OLANZAPINE

Four pivotal clinical trials established the efficacy of olanzapine in treatment of schizophrenia (Tollefson & Kuntz, 1999; Stephenson & Pilowsky 1999). These RCTs compared the drug with either haloperidol or placebo, or both. Both olanzapine and haloperidol were superior to placebo in treating positive symptoms. Olanzapine proved to be better than haloperidol in one of the trials, but both drugs were comparable in the other two studies. Combined results of these trials also demonstrated that olanzapine was significantly more effective against negative symptoms than haloperidol. A post-hoc analysis of the data from one of these trials also concluded that olanzapine was more effective than haloperidol in treating a varied spectrum of patients with schizophrenia with positive, negative or mixed symptom profiles, and a chronic or subchronic course of illness (Gomez & Crawford, 2001). In addition Davis and Chen (2001) carried out a meta-analysis of the data from all four trials. They found that olanzapine produced a greater improvement than haloperidol on a large number of items or factors. EPSEs during olanzapine treatment were indistinguishable from effects seen with placebo. Two studies comparing olanzapine with haloperidol in first-episode psychosis found that although low doses of both drugs were effective olanzapine had a risk benefit profile significantly superior to haloperidol (Sanger et al., 1999; Lieberman et al., 2003). Olanzapine has been found to be efficacious in situations of treatment-resistance compared to haloperidol or chlorpromazine, but results of other studies have been equivocal (Stephenson & Pilowsky 1999).

ZIPRASIDONE

Results from 4-6 week fixed dose RCTs have shown ziprasidone to be superior to placebo and comparable to haloperidol in the treatment of positive, negative, depressive and anxiety symptoms of schizophrenia and schizoaffective disorder (Sartorius et al., 2002; van Kammen & Marder, 2000).

QUETIAPINE

In randomised controlled trials quetiapine has proved to be consistently superior to placebo and effective against both positive and negative symptoms of schizophrenia. Quetiapine was also as effective as chlorpromazine or haloperidol in improving symptoms of acute schizophrenia. The consistent, placebo-level EPSEs associated with quetiapine were not seen with haloperidol. A meta-analysis of data from 4 RCTs has also confirmed the superior efficacy of quetiapine versus haloperidol (Kasper et al., 2001).

ARIPIPRAZOLE

Phase II and phase III trials have shown aripiprazole to be superior to placebo in improving positive and negative symptoms of schizophrenia. The drug was either comparable or somewhat superior to haloperidol in the same studies (Bowles et al., 2003). A meta-analysis of 5 RCTs confirmed the favourable safety and tolerability profile of aripiprazole compared to haloperidol (McQuade et al., 2002).

AMISULPIRIDE

In patients with positive symptoms high doses of amisulpiride produced improvement comparable to haloperidol or flupenthixol. In acutely ill patients it was better than haloperidol or flupenthixol in reducing affective symptoms. Low doses have been shown to be better than placebo or FGAMs in improving negative symptoms (Sartorius et al., 2002). A recent meta-analysis of 18 RCTs found amisulpiride to be better than placebo or FGAMs in treatment of global schizophrenic symptoms and negative symptoms, with fewer dropouts and adverse events (Leucht et al., 2002).

ZOTEPINE

Several RCTs have documented the antipsychotic efficacy of zotepine. It has been better than chlorpromazine in treating psychotic symptoms and has produced less EPSEs than haloperidol (Sartorius et al., 2002; 2003).
SERTINDOLE

Antipsychotic efficacy of sertindole was found to be similar to other SGAMs but it was temporarily withdrawn following concerns about its cardiovascular side effects. The suspension has been lifted and post-marketing surveillance trials have been initiated (Sartorius et al., 2003).

META-ANALYTIC STUDIES

Meta-analyses aggregate the results of individual studies to increase the statistical power, which helps in establishing consistency of treatment effects as well as comparative effectiveness of different drugs.

Cochrane reviews that have compared SGAMs with placebo or FGAMs have found that SGAMS are clearly superior to placebo and mostly equivalent to FGAMs (Sartorius et al., 2003).

Meta-analytic studies focusing on the efficacy of clozapine have found it to be effective in treatment-resistant schizophrenia but the effects are modest and contrary results have also been reported (Wahlbeck et al., 1999; Chakos et al., 2001; Moncrieff, 2003; Tuunainen et al., 2002).

Leucht et al. (1999) conducted a meta-analytic study of efficacy and tolerability of second-generation versus first-generation drugs in treatment of schizophrenia. They found that risperidone, olanzapine, quetiapine and sertindole were all superior to placebo. Sertindole and quetiapine were as effective as haloperidol, whereas olanzapine and risperidone were slightly more effective against global schizophrenic pathology. All SGAMs were superior to placebo in the treatment of negative symptoms, but so was haloperidol. Olanzapine and risperidone were slightly superior, sertindole comparable, and quetiapine less effective than haloperidol in this regard. All SGAMs were associated with fewer EPSEs than haloperidol.

Geddes et al. (2000) carried out a meta-analysis of 52 RCTs comparing SGAMs (amisulpiride, clozapine, risperidone, olanzapine, quetiapine and sertindole) with FGAMs (haloperidol and chlorpromazine). They found substantial heterogeneity in the results partly accounted for by the dose of the comparator FGAM. If the dose of the FGAM was less than 12 mg/day of haloperidol equivalents, SGAMs and FGAMs were comparable in efficacy, although the former still caused fewer EPSEs. They concluded that there were no differences in efficacy and tolerability between the two groups. They proposed that FGAMs should not be used as initial treatments except in cases of previous poor response or unacceptable EPSEs.

Leucht et al. (2002) in a more recent meta-analysis of 18 RCTs comparing amisulpiride with placebo or FGAMs found amisulpiride to be superior to placebo in all aspects. Amisulpiride was more effective against positive symptoms and equally effective against negative symptoms, compared to FGAMs. There were fewer adverse effects and dropouts with amisulpiride.

Another meta-analytic comparison of SGAMs and FGAMs as well as comparison between different SGAMs has been reported recently. RCTs of 10 SGAMs including clozapine, amisulpiride, risperidone, olanzapine, quetiapine, sertindole, zotepine, ziprasidone, remoxipride and aripiprazole, were considered. Only four second-generation drugs clozapine, risperidone, olanzapine and amisulpiride were superior to FGAMs. No differences were found between different second-generation agents. The authors also ruled effects of haloperidol dose as a confounder (Davis et al., 2003).

HEAD-TO-HEAD COMPARISONS

Risperidone and olanzapine have been compared in 2 large RCTs one lasting 8 weeks (Conley & Mahmoud, 2001) and the other 28 weeks (Tran et al., 1997). One found olanzapine to be significantly better in controlling negative symptoms (Tran et al., 1997), the other showed risperidone to be significantly more effective against positive, anxiety and depressive symptoms (Conley & Mahmoud, 2001). In a 4-month open-label comparison of risperidone with quetiapine the only difference that emerged was that patients on quetiapine required less anticholinergic medication (Kasper et al., 2001). A 12-week
RCT of clozapine and risperidone in severe, chronic schizophrenia revealed clozapine to be superior to risperidone, and associated with fewer EPSEs (Azorin et al., 2001). This was similar to the results of an earlier open trial (Flynn et al., 1998) but differed from those of a randomised trial, which found no difference between risperidone and clozapine in treatment-resistant patients (Bondolfi et al., 1998). However the latter trial had several methodological problems. Overall, there is insufficient evidence to demonstrate the superior efficacy of any second-generation agent compared to others.

NEGATIVE SYMPTOMS

The efficacy of SGAMs against negative symptoms of schizophrenia has been demonstrated for a number of drugs including clozapine, olanzapine, ziprasidone, quetiapine, aripiprazole and sertindole (Thomas & Lewis, 1998). These have been supported by meta-analytic data on others such as risperidone or amisulpiride (Carman et al., 1995; Leucht et al., 2002). However, differences compared to first-generation agents are often marginal, and some studies have provided contradictory results. Moreover, it remains unclear whether this effect of SGAMs is a primary one or mediated through improvements in positive symptoms and lack of EPSEs. Carpenter et al. (1995) have distinguished between 'primary' negative symptoms of blunted affect and poverty of speech, from qualitatively similar 'secondary' negative symptoms, which may be the result of severe positive symptoms, depression, or EPSEs. They contend that efficacy against primary negative symptoms are not supported by the current evidence. Some trials (e.g. with olanzapine) have, however, demonstrated otherwise (Tollefson & Kuntz, 1999; Stephenson & Pilowsky 1999).

DEPRESSIVE SYMPTOMS AND SUICIDE

Results of RCTs and several reviews of the subject have suggested that SGAMs have particular efficacy against depressive symptoms that occur as a part of schizophrenia (Levinson et al., 1999; Siris, 2000). Several studies have shown the efficacy of clozapine in reducing suicidality, suicide attempts and mortality from suicide. A recent study attempting to model the impact of increased clozapine prescription on lives saved estimated that if all treatment-resistant patients in the UK received clozapine fifty-three suicides could be avoided each year (Duggan et al., 2003). In another international multi-centric RCT of 980 patients at high risk for suicide (Meltzer et al., 2003), clozapine proved to be superior to olanzapine in preventing suicidal attempts. However, olanzapine has also been shown to significantly decrease suicide risk compared to haloperidol (Tollefson & Kuntz, 1999) and risperidone (Tran et al., 1997).

COGNITIVE SYMPTOMS

Several studies with different second generation agents have shown that as a group SGAMs are more effective than first-generation drugs in improving cognitive function (Sharma, 1999; Bilder et al., 2002), yet again it is unclear whether the improved cognitive profile is a direct effect or secondary to lower treatment-emergent EPSEs with SGAMs (Sartorius et al., 2003).

MAINTENANCE TREATMENT

Trials with several SGAMs including risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole and sertindole have provided evidence for their effectiveness in the long-term treatment of schizophrenia (Sartorius et al., 2002; 2003). However, the number of such studies is still small, some are open-label or extension trials, and others have only considered rehospitalisation rates. Differences compared to FGAMs are inconsistent and marginal. Results of meta-analytic studies have also been contradictory. One recent meta-analysis of 17 relapse-prevention studies of amisulpiride, clozapine, olanzapine, risperidone, ziprasidone, sertindole and zotepine found that SGAMs were superior to placebo in this regard. Further, rates of relapse and overall treatment failure (but not drop outs) were modestly but significantly lower with SGAMs when compared with FGAMs. The evidence was particularly strong for risperidone, olanzapine and sertindole (Leucht et al., 2003). In contrast, another meta-analysis concluded that in the absence of head-to-head trials of appropriate duration the relative efficacy for relapse
prevention of SGAMs against FGAMs remains uncertain (NICE, 2002).

**FIRST-EPISODE PATIENTS**

Randomised controlled trials of clozapine (Lieberman et al., 2003; Woerner et al., 2003) risperidone (Kopala et al., 1997; Emsley et al., 1999) and olanzapine (Sanger et al., 1999; Lieberman et al., 2003) have demonstrated the efficacy of these drugs in first-episode psychosis. However, these are only marginally superior to FGAMs in these situations. Most of these studies suggest that low doses of both first and second-generation agents are effective in first-episode patients. Nevertheless, because of their superior safety in terms of neurological side effects, SGAMS (except clozapine) are recommended for use as first-line treatments and preferred drugs in the treatment of first-episode psychosis (Sartorius et al., 2002; 2003).

**TREATMENT-REFRACTORY PATIENTS**

Although there is some suggestion of efficacy of risperidone and olanzapine in this condition, and despite recent doubts about the effectiveness of clozapine, it still is the drug of choice in these situations (Sartorius et al., 2002).

**ADVERSE EFFECT PROFILE**

The available evidence strongly demonstrates that SGAMs have a lower side effect risks in terms of EPSEs, TD and in most cases elevation of prolactin and consequent endocrine effects, than FGAMs. However, this advantage can often be offset by troublesome side effects such as weight gain, and potentially serious metabolic, cardiovascular and haematological effects (Sartorius et al., 2002; 2003).

**COMPLIANCE/PATIENT PREFERENCE/QUALITY OF LIFE**

It is probably because of this favourable side effect profile that differences are seen between first and second-generation agents in terms of improved compliance, increased patient preference and better quality of life (Sartorius et al., 2003; Dolder et al., 2002).

**COST-EFFECTIVENESS**

The evidence regarding cost-effectiveness of SGAMs (or the lack of it) is still a matter of some debate. Although the cost per-tablet basis of second-generation drugs is substantially higher, the total costs of treatment appear to be lower than FGAMs. The lower risks of EPSEs and improved quality of life with SGAMs may prove advantageous in cost-effectiveness terms, but these parameters are often not entered into cost-benefit analyses (Sartorius et al, 2003).

**SIDE EFFECTS**

**SEDATION**

Sedation is the most common adverse effect of clozapine and is also observed with a number of other drugs including olanzapine, risperidone, ziprasidone and quetiapine (Barnes & McPhillips, 1999).

**POSTURAL HYPOTENSION**

Postural hypotension and giddiness is often reported by patients on clozapine, and is also commonly associated with risperidone, olanzapine, quetiapine and sertindole (Barnes & McPhillips, 1999).

**SIALORRHOEA**

Hypersalivation during sleep and other times is a particularly troublesome side effect of clozapine. It can be treated with low doses of amitriptyline or clonidine (APA, 1997; Barnes & McPhillips, 1999).

**SEIZURES**

This is a serious side effect of clozapine. The incidence is dose related with maximum risk (4.4%) at doses greater than 600mg/day. Most patients who experience a seizure are, however, able to
continue clozapine after dose reduction, gradual re-challenge, or addition of an anticonvulsant. Though any of the other drugs can also induce seizures risperidone, olanzapine, quetiapine and sertindole have shown no increase in risk compared to haloperidol or placebo (Barnes & McPhillips, 1999).

NEUTROPENIA/AGRAINOCYTOSIS

A potentially fatal side effect seen with clozapine is agranulocytosis (reduction of absolute neutrophil counts below 500 mm3). The risk is about 0.8% worldwide and greatest during the first 3 months of treatment. Risk factors include increasing age, female gender, Asian origin, and low neutrophil counts before treatment (Barnes & McPhillips, 1999). Detailed guidelines regarding monitoring for and management of clozapine-related agranulocytosis are available (APA, 1997; van Kammen & Marder, 2000). Several cases of olanzapine-related neutropenia/ agranulocytosis have been reported recently. This has often been seen in patients who had a prior history of clozapine-related neutropenia. It is now recommended that white blood cell counts be monitored in patients on SGAMs who have a history of drug-induced white cell disorders, or are on drugs which could cause such disorders (Sartorius et al., 2003).

WEIGHT GAIN

Weight gain is seen with almost all second-generation drugs with the exception of ziprasidone. In one of the most detailed meta-analytic reviews of the subject Allison et al. (1999) showed that the magnitude of weight gain was greater among SGAMs. Clozapine and olanzapine were associated with the highest gain in weight, and ziprasidone the least. Though patients gain weight early in treatment, some amount of weight gain continues throughout treatment. Weight gain is not dose dependent. Gain in weight is often associated with a number of adverse physical and psychosocial outcomes. Treatment is recommended if a patient gains 2.3 kgs or more. Periodic monitoring, recommendations regarding diet and exercise form the basis of such treatment. The role of weight reducing drugs such as sibutramine is uncertain (Allison et al., 1999; Allison & Casey, 2001; Blackburn, 2000).

HYPERPROLACTINEMIA

Most SGAMs do elevate prolactin levels, although not to the same extent as first-generation drugs. The elevations are significantly above baseline in case of risperidone and amisulpiride, but minimal with clozapine, olanzapine, quetiapine and aripiprazole (Sartorius et al., 2002; 2003). Hyperprolactinemia can be associated with amenorrhea, galactorrhea, and sexual dysfunction (Wieck & Haddad, 2003).

SEXUAL DYSFUNCTION

Although the extent of the problem is not clearly known, SGAMs do cause all manner of male and female sexual dysfunctions. Whether the rates of these side effects are similar for both first and second-generation drugs, as some studies seem to suggest, is also not clear (Sartorius et al., 2002; 2003).

DIABETES MELLITUS/HYPERLIPIDEMIA

Based on several reports there has been growing concern about the risks of new-onset diabetes and disturbances in lipid metabolism associated with second-generation agents. Some studies have reported the risk of diabetes to be greater among patients receiving SGAMs, while others have been unable to find significant differences between FGAMs and SGAMs. Among the SGAMs clozapine and olanzapine carry the highest risk of new-onset diabetes. The risk appears to be greater in younger patients below 40 years of age. The data suggests that SGAMs like clozapine or olanzapine rather than causing diabetes/hyperlipidemia independently, may induce these disorders in susceptible persons (Henderson et al., 2000; Lund et al., 2001; Sernyak et al., 2002; Koro et al., 2002). The medical consequences of these effects are not clear. Monitoring of these parameters in those at risk is required during treatment (NICE, 2002; APA, 2004).
EPSES

As a group second-generation antipsychotics are much less likely to cause EPSEs than FGAMs. However, SGAMs vary considerably in their propensity to cause various EPSEs. A dose dependent effect has been observed with risperidone, with doses more than 6 mg/day more likely to cause EPSEs. High doses of amisulpride are also known to cause similar effects. On the other hand drugs like quetiapine, aripiprazole, olanzapine and clozapine carry almost no risk of causing EPSEs. The risks of TD are also considerably less among all SGAMs. Then again there are several case reports of TD with all SGAMs and akathisia with clozapine (Sartorius et al., 2002; 2003). A recent review also identified several instances of NMS occurring with clozapine and risperidone (Hasan & Buckley, 1998).

CARDIOVASCULAR SIDE EFFECTS

Tachycardia is a common side effect of clozapine and sertindole and has been reported with quetiapine. Cohen et al. (2001) reported that clozapine was significantly more likely than haloperidol to cause higher heart rate, lower heart rate variability and other indicators of autonomic dysregulation and impaired cardiac repolarisation. There are also recent reports of clozapine-related myocarditis and cardiomyopathy in physically healthy young adults started on treatment. All SGAMs prolong the QTc interval and this effect has raised some concerns in case of ziprasidone and sertindole (Sartorius et al., 2003; Barnes & McPhillips, 1999). The latter was briefly withdrawn because of concerns regarding its cardiovascular safety profile.

OTHER SIDE EFFECTS

Other side effects of SGAMs include nasal congestion with risperidone and sertindole, raised liver transaminases with olanzapine, urinary incontinence with clozapine and risperidone etc. (Barnes & McPhillips, 1999).

MAINTENANCE TREATMENT WITH ANTIPSYCHOTICS

FGAMS

Efficacy

Several RCTs and systematic reviews have provided strong support for the efficacy of first-generation antipsychotics in relapse prevention. In the most comprehensive study of this subject Gilbert et al. (1995) analysed the results of 66 studies involving 4365 patients of schizophrenia. The mean cumulative relapse rate was 53% in patients withdrawn from treatment and 16% in those maintained on drugs over a mean follow-up period of 9.7 months. The only consistent predictor of relapse was the length of follow-up. Others have found that relapse in patients withdrawn from antipsychotics occurs relatively early, usually within the first 3 months after stopping drugs. Relapse rates are higher in those patients whose drugs are withdrawn rapidly (Baidessarini & Viguera, 1995). The review by Gilbert et al. (1995) also highlights the dilemmas in maintenance treatment. About half of the patients in their review managed to remain relapse free even after their drugs were withdrawn, although others have argued that this was due to the short length of follow-up and almost all(518,202),(583,225)(497,202),(561,225)(185,202),(249,225) patients whose drugs are withdrawn rapidly (Greden & Tandon, 1995). There is, however, the problem of a significant minority of patients (16% in Gilbert’s review) who relapse despite continuing with treatment. Further, there are no reliable ways to predict this relapse. On the other hand, continued treatment with FGAMs takes its toll in terms of side effects and increases the risk of producing TD (Gilbert et al., 1995).

DOSING STRATEGIES

Studies have looked at the differential efficacy of high, standard, low and very low doses of antipsychotics during maintenance treatment. Another strategy that has received some attention is that of targeted or intermittent therapy.
HIGH DOSE THERAPY

A review of 33 RCTs in which high doses (mean of 5200 mg of chlorpromazine equivalents) were compared with low dose (mean of 400 mg chlorpromazine equivalents) found that lower doses had superior efficacy as well as tolerability (Baldessarini et al., 1988).

STANDARD DOSES

This essentially refers to the doses normally used to treat patients during acute phases. In most trials this would be about 25-50 mg of fluphenazine decanoate or 40 mg of flupenthixol decanoate every 2 weeks, or 100 mg of haloperidol decanoate every month. The efficacy of these doses in relapse prevention is beyond doubt. However, the burden of side effects, the risk of TD, expectations of patients and relatives regarding dose reduction have prompted the examination of other dosing strategies which utilize lower doses (Johnson, 1985; Schooler, 1993; Kane, 1995; Kane, 1999).

LOW DOSES (OR CONTINUOUS LOW-DOSE TREATMENT)

In the various trials conducted low doses have been of the order of 2.5-5 mg of fluphenazine decanoate or 20 mg of flupenthixol decanoate every 2 weeks, or 50 mg of haloperidol decanoate every month. The results of some of these studies suggest that dose reduction is feasible. Short-term (up to about a year) relapse rates are not significantly different between the low dose and standard dose groups. Positive effects of dose reduction are evident in the diminution of side effects, particularly EPSEs, and reduction in anxiety and depressive symptoms. Family members are more satisfied with the outcome of dose reduction and family burden is less with low doses. However, reduction in risk of TD is not consistently or clearly evident. On the other hand the risk of psychotic relapses can be greater with lower doses. The proportion of patients relapsing increases with lower doses and longer periods of follow-up. The more unstable the patients are initially, the greater the risk may be. Apart from this it is difficult to predict which patient will, or will not benefit from dose reduction (Johnson, 1985; Schooler, 1993; Kane, 1995; Kane, 1999).

This has led several authors to conclude that dose reduction, even in clinically stable patients, is problematic and difficult to justify (Schooler et al., 1997; Kane et al., 2002).

VERY LOW DOSES

Very low doses of antipsychotics (less than 5 mg of fluphenazine decanoate or 25 mg of haloperidol decanoate) have been used in some studies for maintenance treatment. Very low doses lead to a significantly higher relapse rate in the first year of follow-up (Kane et al., 1983; 2002).

TARGETED OR INTERMITTENT TREATMENT

Targeted or intermittent strategies involve discontinuation of medication followed by intensive monitoring to identify the earliest signs of exacerbation or relapse, at which point treatment is immediately reinstated. Studies show that such strategies are feasible and can be implemented in outpatient settings. They result in reduced cumulative antipsychotic exposure and reduction in side effects. However, the high rates of relapse and rehospitalisation make this an unacceptable option. This strategy is only recommended for patients who refuse continuous medication and might comply with an intermittent regimen if properly educated (Johnson, 1985; Schooler, 1993; Kane, 1995; Kane, 1999).

DURATION OF TREATMENT

Studies suggest that the duration of treatment in patients who have had multiple exacerbations or relapses should be five years or longer (Johnson, 1985). For first-episode patients medications need to be continued for at least one year (Johnson, 1985), although some studies suggest that maintenance treatment needs to continue beyond this period (Gitlin et al., 2001).
side effects, especially TD. This is less of a problem with second-generation drugs. Thus continuous maintenance treatment with a SG AM may be the best option for preventing relapse. Although, controlled trials have indicated that these drugs can be used in maintenance treatment, the evidence is limited and conflicting (NICE, 2002; Sartorius et al., 2003).

DEPOT ANTIPSYCHOTIC TREATMENT

The introduction of depot antipsychotics in the 1960s was heralded as a major advance in the treatment of chronic schizophrenia. Depot antipsychotics generally consist of an ester of the drug in an oily solution, which is administered by deep intramuscular injection. Following injection, the drug is slowly released from the injection site allowing relatively stable plasma drug levels to be achieved over long periods, while injections only need to be given once every few weeks. Depot injections guarantee consistent drug delivery, overcome the bioavailability problems that occur with oral preparations, and eliminate the risk of deliberate or inadvertent overdoses. There is less inter-individual variability and patients can be treated with lower doses. However, the main practical advantage is the avoidance of covert non-adherence with drug treatment. People on depots need to attend a clinic regularly to receive their injection and can be closely supervised during this process. Any drop outs are immediately identified and steps taken to intervene early.

The disadvantage of depot preparations is the comparative lack of flexibility of administration, with adjustment to the optimal dosage being a protracted and uncertain process. They have the potential to cause more adverse effects such as EPSEs including TD and can be associated with uncomfortable reactions at the site of injection. Patients sometimes resent this form of treatment. Finally, their use does not always guarantee good treatment adherence, with around a third of those prescribed depots failing to become established on the injections (Johnson, 1985; Kane, 1995).

Over the years a substantial body of literature has accumulated examining the efficacy and safety of depot injections versus oral drugs. Initial trials, reviews and meta-analyses concluded that patients maintained on depots had a significantly lower rate of relapse than those on oral medication. The risk of adverse effects was no greater when comparisons were made with equivalent doses of oral antipsychotics. The number of refusals was small and rates of non-compliance a fraction of those defaulting on oral drugs (Johnson, 1985; Kane, 1995). More recently, larger and more comprehensive meta-analytic reviews have suggested otherwise. Depots appear to be safe and effective modes of treatment, not associated with any greater risks of treatment-emergent side effects. However, they confer only a small benefit over oral medication in terms of global improvement. There are no differences between depot and oral antipsychotics in terms of relapse rates or dropouts. Comparison between different depots revealed a small advantage for zuclopenthixol decanoate in terms of lower relapse rates, but this could be due to the fact that it is a comparatively newer compound. Similarly, fluphenazine preparations were associated with a higher risk of EPSEs, probably as a result of the larger number of trials with these injections. Evidence in favour of cost-effectiveness of depots was little and of uncertain value (NICE, 2002; Adams et al., 2001). Then again, another systematic review of patient attitudes found that patients were happy with their depot treatment and preferred it to oral medication (Walburn et al, 2001).

Until recently there were no depot preparations of second-generation antipsychotics, which was a major disadvantage of these drugs. A long acting form of risperidone has now become available. Moreover, a 12-week multicentric double-blind randomised placebo controlled study of 554 patients has shown that 25 mg. of depot risperidone administered every 2 weeks is a safe and efficacious means of treatment (Kane et al 2003).

RAPID TRANQUILLISATION

Acute behavioural disturbances in the context of schizophrenia may require urgent treatment. A person may be agitated, aggressive or violent towards others as a result of persecutory delusions,
command hallucinations, or high levels of anxiety. Rapid tranquilisation means the use of drug treatments to achieve rapid, short-term behavioural control of extreme agitation, aggression and potentially violent behaviour that places the individual or those around them at risk of physical harm. The aim of drug treatment in such circumstances is to calm the person, and reduce the risk of violence and harm, rather than treat the underlying psychiatric condition. An optimal response would be a reduction in agitation or aggression without sedation (NICE, 2002; McAllister-Williams & Ferrier, 2002).

Parenteral preparations useful in rapid tranquilisation are i.m. injections of lorazepam, haloperidol, olanzapine or ziprasidone, and i.v. preparations of lorazepam, diazepam or haloperidol. Intramuscular chlorpromazine is not recommended because of potentially serious cardiovascular side effects, i.m. droperidol has been withdrawn because of similar concerns, and i.m. diazepam is not used due to its erratic absorption (McAllister-Williams & Ferrier, 2002).

Data on comparative effectiveness of these drugs is limited, and there appear to be no clinically significant differences between benzodiazepines and antipsychotics. However, recent reviews have suggested that a combination of i.m. haloperidol and i.m. lorazepam may produce a faster response than i.m. haloperidol alone (NICE, 2002). Three RCTs have also shown i.m. olanzapine to be as effective as, and have a better side effect profile than i.m. haloperidol. Some studies have also found i.m. ziprasidone to be rapidly effective and well tolerated at therapeutic doses with minimal EPSes (Sartorius et al., 2003; McAllister-Williams & Ferrier, 2002). In practical terms steps should be taken to anticipate possible violence and to de-escalate the situation at the earliest opportunity. Physical means of restraint or seclusion should be resorted to only after the failure such of attempts. When drugs have to be used low doses of single agents are preferred. Oral medication (tablets, rapidly dissolving formulations and liquids) should be offered before parenteral medication. If parenteral treatment proves necessary, the i.m route is to be preferred over the i.v. one from a safety point of view. Intravenous administration should only be used in exceptional circumstances. When rapid tranquilisation is urgently needed, a combination of i.m haloperidol and i.m lorazepam can be considered. Regular monitoring for adverse consequences is essential. Staff should be trained in this method, and there should be adequate access to facilities for resuscitation (NICE, 2002; King, 1995; McAllister-Williams & Ferrier, 2002).

ADJUNCTIVE MEDICATION

LITHIUM CARBONATE

Most trials of lithium in schizophrenia have been carried in the acute phase of the illness, and controlled data is scarce. Studies of lithium as monotherapy in schizophrenia show only modest improvements, sometimes even worsening of symptoms, and early relapses with the drug. Lithium is less efficacious than FGAMs in this situation. However, when added to antipsychotic medications lithium augments the response in general, and appears to specifically improve negative symptoms. Such improvement is greatest in the areas of psychotic symptoms, agitation and excitement, irritability, and behavioural and functional disturbances. Such improvement can be seen in up to half of the patients, so a trial of adjunctive lithium needs to be considered in patients who show poor response to antipsychotics (APA, 1997; Siris, 1993; Morrison, 1996; Barnes et al., 1996; Williams et al., 2002). Lithium has also been shown to have specific benefits for patients of schizophrenia with affective symptoms. Lithium either alone or added to FGAMs shows greater ability to reduce depression/anxiety and thought disorders scores in patients of schizophrenia with depression. Such effects are not seen in patients who are not depressed. Indirect evidence for efficacy of lithium in schizophrenia with affective symptoms comes from trials showing the usefulness of lithium-antipsychotic combinations in schizoaffective disorder (APA, 1997; Siris, 1993; Morrison, 1996; Barnes et al., 1996; Williams et al., 2002). However, a recent review concluded that adjunctive use of lithium for depressive symptoms in schizophrenia is inadequate and inconsistent, and there is no empirical basis for its use in such conditions (Levinson et al., 1999).
There has been some concern about adverse effects of lithium-antipsychotic combinations, particularly neurotoxicity. Though estimates vary, neurotoxic effects are generally uncommon under ordinary therapeutic conditions. Nevertheless, monitoring for such side effects and regular serum-level estimations are recommended. A trial of 4-12 weeks is required to determine the response to lithium when added to an antipsychotic. Predictors of a favourable response include excitement, overactivity, affective symptoms, especially depression, episodic course and past or family history of affective symptoms (APA, 1997; Siris, 1993; Morrison, 1996; Barnes et al., 1996; Williams et al., 2002).

ANTIDEPRESSANTS

It is generally recognized that a substantial proportion of patients with schizophrenia suffer from either depressive symptoms or clinically significant depressive episodes, during various phases of their illness. However, the treatment of depression in schizophrenia is complicated by difficulties in distinguishing symptoms from syndromes, depressive symptoms from negative symptoms and EPSEs, and concerns about exacerbations of psychosis with antidepressants. The large majority of studies examining adjunctive antidepressant treatment in schizophrenia have involved addition of tricyclic drugs or monoamine oxidase inhibitors to FGAMs. These have often, but not always, indicated that the addition of such drugs to ongoing antipsychotic treatment produces substantial benefits. Two recent reviews have also concluded that there is substantial evidence to indicate that adjunctive antidepressants are useful in treatment of depressive syndromes, but not depressive symptoms, in the post-psychotic phase. At the same time they have cautioned against the use of additional antidepressants during acute exacerbations of schizophrenia because of the lack of efficacy, and potential for worsening psychotic symptoms (Levinson et al., 1999; Siris, 2000).

The evidence for efficacy of antidepressants in treatment of other syndromes such as negative symptoms or anxiety syndromes is sparse, mostly inconsistent, and generally inconclusive (APA, 1997; Siris, 1993; Morrison, 1996; Barnes et al., 1996; Williams et al., 2002).

BENZODIAZEPINES

A meta-analytic review of double-blind trials of adjunctive benzodiazepine treatment in schizophrenia showed that addition of benzodiazepines to antipsychotics had positive effects on anxiety, agitation and positive symptoms. Responses are seen in about half of the treated patients. This strategy appears to be particularly useful in the management of acute psychotic agitation, because of the sedative effects of benzodiazepines, and rapid onset of beneficial effects. Benzodiazepine use has the added advantage of reduction in antipsychotic doses and consequent relief from antipsychotic-related side effects. However, other studies have indicated that effectiveness of benzodiazepines does not last beyond the first few weeks.

Limited evidence also suggests that adjunctive benzodiazepine treatment may be specifically useful in patients with either prominent anxiety symptoms or comorbid anxiety syndromes.

The evidence for efficacy of adjunctive benzodiazepines in the management of negative or depressive symptoms is limited and contradictory. Benzodiazepines as monotherapy in schizophrenia have only mild antipsychotic efficacy, and are inferior to FGAMs in this regard. Paradoxical disinhibition, worsening of symptoms on benzodiazepine discontinuation, and instances of abuse/dependence have been reported (APA, 1997; Siris, 1993; Morrison, 1996; Barnes et al., 1996; Williams et al., 2002).

ANTICONVULSANTS

Double-blind studies of adjunctive carbamazepine in acute phase of schizophrenia have shown significant positive effects. Such treatment appears to produce improvements in patients who are agitated or violent, and those who have EEG abnormalities suggestive of seizure activity. The number of such studies is, however, still very small and most studies have a number of methodological
problems. Studies with other anticonvulsants are still fewer. A review of five studies of valproate in schizophrenia concluded that there is little evidence for its efficacy. When treating patients with additional carbamazepine or valproate, the dose of the antipsychotic might need to be adjusted because these drugs can reduce blood levels of antipsychotics (APA, 1997; Siris, 1993; Morrison, 1996; Barnes et al., 1996; Williams et al., 2002).

**ELECTROCONVULSIVETHHERAPY**

In the acute phase of schizophrenia some studies of first-admission patients have found ECT alone to be as effective as first-generation antipsychotics. However, one RCT of first-admission patients found that while ECT alone was superior to psychological therapies, it was not as effective as antipsychotics alone. On the other hand, when ECT is combined with antipsychotics the combination has been consistently more effective than either treatment used alone. Combinations of ECT and antipsychotics also result in more rapid resolution of symptoms. It is equally effective in ameliorating both affective and psychotic symptoms. If used during the initial part of the illness ECT can reduce risks of chronicity and further personality deterioration. A short duration of illness predicts better response. ECT is also useful in treatment of patients with catatonic or depressive presentations and those at risk for suicide. However, the acute efficacy of ECT/antipsychotic combinations is not maintained for long, and advantages disappear within a matter of weeks (APA, 1997).

In chronic schizophrenia ECT is much less effective and response rates in patients continuously ill for more than a year are 20% or less. There are very few controlled studies of the role of ECT in treatment-refractory patients. Uncontrolled data have shown some benefits of ECT when used alone in patients with poor response to drugs, or in combination with FGAMs and clozapine in patients resistant to treatment (APA, 1997).

**MODALITIES OF TREATMENT - SOMATIC**

1. **Antipsychotic medications**
   - First-generation antipsychotic medications
   - Second-generation antipsychotic medications
   - Oral/parenteral/depot - preparations

2. **Adjunctive medications**
   - Lithium carbonate
   - Antidepressants
   - Benzodiazepines
   - Anticonvulsants

3. **Other medications**
   - Antiparkinsonian medications
   - Beta-blockers

4. **Electroconvulsive therapy**

**PSYCHOSOCIALTREATMENTS**

Although the causes of the schizophrenic syndrome remain unclear, most workers in this field view it from stress-diathesis or bio-psychosocial perspective. Apart from emphasising the underlying biological vulnerabilities, this model also stresses their interaction with psychological and social factors in the onset and course of the disorder (Zubin, 1986). Research over the years has delineated a number of these psychosocial factors such as stressful life events, expressed emotion, and social support. Specific interventions designed to target some or all of these parameters have proved useful.
in improving the outcome of schizophrenia.

The need for psychosocial therapies is being increasingly acknowledged for several reasons. Although pharmacotherapy is effective in treating acute symptoms and reducing the risk of relapse, it is not always effective, neither does it guarantee good outcome all the time. Drugs do not address the problem of residual social and cognitive deficits to the same extent as symptom relief. Drugs cannot teach a patient the skills required to cope with the demands of daily living. Nor can they wholly alleviate the distress of relatives or reduce the burden of caring for an ill family member. Drug compliance is a major problem, as is relapse, which can be precipitated by family/environmental factors.

In contrast, psychosocial treatments extend beyond symptoms of the illness and encompass the pervasive deficits in social, cognitive, and affective domains; as well deficits in daily functioning that are characteristic of schizophrenia. They help prepare patients and their families to cope with the illness, help patients strive for greater self-sufficiency and achieve a better quality of life. In addition, these therapies seek to enhance treatment adherence, to decrease distress and disability, to minimise symptoms, and to reduce risk of relapse in patients. Finally, such treatments also endeavour to reduce distress and burden among family members (Penn, & Mueser, 1996; Stillo et al., 2001; Garety, 2003).

The term 'psychosocial treatments' refers to all those procedures, psychological or social, used to intervene on behalf of the patient. Specifically, it excludes somatic treatments (Lehman, 1995). Psychosocial interventions can be classified according to their focus, modus, or locus, as well as their goals and objectives. The focus may be the individual, his family, groups, or the whole milieu. The modality of treatment varies from psychodynamic to behavioural, or a combination of several strategies. The locus can be an inpatient facility, a day hospital, a social club etc. Each intervention often has different goals or objectives. For example, some may maintain the individual at a marginal level of functioning with minimal stress or relapse, while others may aim to teach him social and independent living skills. However, these interventions are not substitutes for somatic treatments. Rather, they complement and add to the benefits obtained by drugs. Sufficient evidence exists to suggest that best results are obtained by using a combination of pharmacotherapy and psychosocial measures. (Lehman, 1995; Penn, & Mueser, 1996).

**FAMILY INTERVENTION**

This includes all family intervention programmes, which involve a combination of didactic materials about schizophrenia for patients and their relatives, and therapeutic strategies designed to improve stress management by all family members through enhanced communication and problem solving skills. These programmes evolved from research originating in Britain about the concept of expressed emotions (EE), which has been subsequently replicated in other countries. The common goals of all these programmes include decreasing patient relapses, decreasing family burden, and improving both the patient's and family's functioning. All approaches emphasise the value of family participation in treatment and stress the importance of working together in a collaborative process.

Common elements of such interventions include positive and early engagement, ongoing contact, education about aetiology, treatment, and prognosis of schizophrenia, teaching coping with stress, increasing problem-solving and communication skills, and crisis intervention. Other components often incorporated are identification of stressors associated with relapse, setting of realistic expectations, expanding social networks etc. (Penn, & Mueser, 1996; Stillo et al., 2001; Garety, 2003).

There are several systematic reviews of controlled trials comparing family intervention with other forms of care, mainly standard outpatient care and also supportive psychotherapy, psychoeducation etc. The more recent meta-analyses have included up to 18 such RCTs (NICE, 2002). There is strong evidence from this data that family treatment improves the outcomes for people with schizophrenia living with, or having close contact with, their family, most notably in reducing the rate of psychotic
relapses both during treatment and for up to 15–24 months after treatment has ended. Family interventions are also effective in reducing relapse rates in those who have recently relapsed, and in those who remain symptomatic after resolution of an acute episode. The benefits are most marked if treatment is provided over a period of more than 6-9 months and/or for more than 10 planned sessions, and if the patient is included in the family sessions. Family interventions also decrease family-burden and improve treatment adherence. Their effects on social functioning are less clear. They do not seem to influence symptoms, suicide rates, or rehospitalisation rates. All modes of delivering treatment are equally efficacious though patients seem to prefer single-family rather than multiple-family interventions. Limited evidence also suggests that providing family interventions may represent good 'value for money' (NICE, 2002; Penn, & Mueser, 1996; Stillo et al., 2001; Garety, 2003; Pilling et al., 2002).

However, despite consistent results across diverse interventions, the components critical to the success of family interventions have not yet been identified. Little is known about the characteristics of patients or families who do, or do not respond to such treatments. Research is also needed to clarify the relative cost-effectiveness of different models of family treatment for differing patient groups and types of problems (Lehman, 1995).

COGNITIVE BEHAVIOURAL THERAPY

Cognitive behavioural therapy (CBT) was originally developed in the 1970s for the treatment of depression, and has since been applied to a large number of different clinical conditions. CBT for psychotic disorders was a later development, informed by new cognitive psychological models of positive psychotic symptoms. Its initial focus was on patients with persistent psychotic symptoms, but its use has been extended later to other groups of patients with schizophrenia. Controlled trials have also tried to address outcomes other than symptom reduction. In the management of schizophrenia, CBT has been applied in a variety of different ways with a number of different aims; common to all are attempts to modify psychotic experiences/ symptoms or their effects upon a person's thoughts, feelings and/or behaviour. CBT bases itself on a collaborative effort with the patient to make sense of his/her psychotic experiences. This involves identifying key beliefs, and thoughts, reviewing the evidence for these, becoming aware of thinking biases, and relating thoughts to mood and behaviour. Patients are encouraged to try out new ways of behaving or thinking in 'homework' sessions. Although CBT is delivered in a structured and time-limited way, the standard cognitive therapy approach is modified to meet needs of people with psychosis. Modifications include longer duration during the early part of treatment and flexibility regarding sessions, to allow engagement and prevent therapy from becoming too stressful (Garety, 2003).

Several reviews of efficacy of CBT have been carried out including a recent meta-analysis of 13 RCTs (NICE, 2002). All participants in these trials were also receiving antipsychotic drugs, and most often CBT was targeted at individuals with long-standing or treatment-resistant psychosis. Control groups received 'standard care', recreational activities, befriending or supportive counselling. Overall, there was strong evidence to suggest that CBT reduces symptoms for people with schizophrenia during treatment and at 9-12 month follow-up, compared to 'standard care' and other treatments. The evidence was stronger when CBT was used for the treatment of persisting psychotic symptoms rather than for acute symptoms. The evidence for the use of CBT in the acute phase of a first episode of schizophrenia was unclear. CBT can also improve insight and adherence with drug treatment and may have a positive effect upon social functioning. The benefits of CBT are most marked when treatment is continued for more than 6 months and involves more than 10 treatment sessions. Shorter-term treatment with CBT may produce modest improvements in depressive symptoms, but is unlikely to have an impact upon psychotic symptoms. Moreover, when CBT is continued for longer than 3 months, there is stronger evidence that relapse rates are reduced. The available evidence suggests that CBT may be more cost effective than other control treatments, but is not conclusive. At the same time the quality of RCTs has been criticized, and the better-designed trials have been unable to demonstrate

(34)
superiority of CBT over other control treatments. Since CBT is a relatively newly developed treatment option in the management of schizophrenia, further research into the use and effects of CBT in the treatment of people with schizophrenia is needed to clarify the different roles and potential value of this treatment (NICE, 2002; Stillo et al., 2001; Garety, 2003; Pilling et al., 2002).

SOCIAL SKILLS TRAINING

This is a highly structured approach, which uses behavioural and learning techniques to target the social disabilities accompanying schizophrenia. The goal is to remedy specific deficits in the patient's role functioning by helping him to acquire skills required to meet interpersonal, self care and other coping demands of community life. Social skills training programmes begin with a very detailed assessment and

behavioural analysis of individual social skills. Skills are then taught through a combination of positive reinforcement, goal setting, modelling, role-playing, rehearsal, coaching, reinforcement, shaping etc. The type of skills vary widely and usually include communication, assertiveness and problem-solving skills, or skills related to certain activities of daily living such as managing medication, shopping, transport, cooking etc. The training can be imparted in either individual or group settings with patients and/or their families. Initially smaller social tasks, such as responses to non-verbal social cues, are worked-on, and gradually new behaviours are then built-up into more complex social skills such as conducting a meaningful conversation. There is a strong emphasis on homework assignments to help generalise newly learnt behaviour away from the treatment setting (Penn, & Mueser, 1996; Stillo et al., 2001).

Several reviews and meta-analytic studies have demonstrated that skills training has an effect on improving the specific social skills targeted during treatment, and that this learning can be maintained for up to 12 months. However, there is little evidence that this learning translates into improved social outcomes in terms of improvement in social functioning, competence or adjustment. This lack of generalization of skills from treatment settings to community settings is a major limitation of this treatment. There is also very little evidence to suggest that social skills training benefits symptoms or reduces relapse rates (NICE, 2002; Penn, & Mueser, 1996; Stillo et al., 2001; Pilling et al., 2002).

COGNITIVE REMEDIATION

Cognitive remediation techniques for schizophrenia have been based upon comparable methods of treatment in people with neurological disorders. The major methods concentrate on repeating laboratory-based cognitive tests or repeated practice of procedures designed to specifically address a particular cognitive deficit. The theory behind this approach asserts that cognitive deficits contribute to a person's vulnerability to schizophrenia (either directly or through increasing a person's susceptibility to stress), and therefore correcting these deficits should, at least in theory, render a person less vulnerable (NICE, 2002; Penn, & Mueser, 1996; Stillo et al., 2001).

Although initial studies demonstrated that certain cognitive processes such as attention/concentration or executive functions might be amenable to such treatment, recent meta-analytic evidence is disappointing. This shows no consistent evidence that cognitive remediation is effective in improving outcomes for people with schizophrenia, either in terms of specially targeted cognitive functions, or in terms of core outcomes such as symptom reduction (NICE, 2002; Penn, & Mueser, 1996; Stillo et al., 2001; Pilling et al., 2002).

INDIVIDUAL THERAPY

Exploratory insight oriented psychotherapy has not proved very useful in treatment of schizophrenia. Supportive therapy or supportive counselling is thus the most widely accepted and practiced form of psychotherapy. It usually consists of empathic listening, active problem solving, education about the illness and its treatment, and developing a supportive relationship. The major problem with the technique
is that its use in schizophrenia remains undefined, and research evidence for its efficacy is scant (APA, 1997; Penn, & Mueser, 1996; Stillo et al., 2001).

The only meta-analysis of this area defined supportive therapy very clearly and examined the results of 14 RCTs comparing it with other types of treatment (NICE, 2002). There was no evidence to suggest that supportive psychotherapy was superior to 'standard care' or 'other active treatments' in the treatment of people with schizophrenia. Nevertheless, certain potential benefits of such therapy such as reducing distress, enhancing compliance, and gaining a better understanding of the patient are, however, quite evident in routine practice. Moreover, the role of a supportive empathic relationship between a person with schizophrenia and a professional, in which good listening plays a central role in the therapeutic alliance is an essential part of good practice (APA, 1997; NICE, 2002).

GROUP THERAPY

Apart from social skills training and family psychoeducation groups, a variety of other group therapies ranging from psychotherapeutic to educational and supportive, have been used in the treatment of schizophrenia. The goals of group therapy are similar to individual supportive treatment, such as improving social functioning or learning to deal with the illness. As with individual therapy, evidence for the efficacy of group treatments is at best modest. Moreover, a number of these studies are plagued by serious methodological flaws (APA, 1997; Penn, & Mueser, 1996).

SPECIFIC PROGRAMMES FOR EARLY INTERVENTION

Specific programmes that target prodromal symptoms can be useful in preventing relapse. A few RCTs have shown specific attempts to educate patients/relatives about prodromal symptoms and early intervention can reduce relapse rates (APA, 1997).

VOCATIONAL REHABILITATION

Unemployment rates among severely mentally persons are extremely high mainly because of the associated disability, and partly due to factors such as stigma, discrimination, and the low priority given to employment status by mental health services. Nevertheless, work and employment schemes (or vocational rehabilitation) have been developed motivated by the belief that work can itself be therapeutic, and can help patients develop skills and gain the confidence to re-enter competitive employment.

Two models of vocational rehabilitation have emerged over recent years, each using differing methods and principles, both aiming to improve employment outcomes. These are:

Pre-vocational Training: - in which participants are expected to undergo a period of preparation before being encouraged to seek competitive employment. This preparation phase could involve either work in a sheltered environment (such as a workshop or work unit), or some form of pre-employment training (e.g. job support or job clubs), or transitional employment.

Supported Employment: - which is an approach to vocational rehabilitation that attempts to place clients immediately in competitive employment. Supported employment can begin with a short period of preparation, but this does not usually involve work placement in a sheltered setting, or training, or transitional employment.

There is evidence from several (mostly US) studies to suggest that supported employment is superior to pre-vocational training programmes in helping people with serious mental health problems gain competitive employment (NICE, 2002; Stillo et al., 2001).

COMMUNITY INTERVENTIONS

CASE MANAGEMENT

Patients of schizophrenia are often ill prepared to find and maintain links with multiple services they need to function in community. Case management is the attempt by one person (the case (36)
manager) or a team of professionals (outreach teams) to ensure that such patients receive coordinated, comprehensive and continuous care. There are several models of case management. In the 'brokerage' model the primary role of the case manager is to help the patient establish contact with various services, and coordinate between different service providers. In the clinical case management model managers are clinicians who apart from brokering, act as clinicians and provide direct services. Assertive Community Treatment (ACT) is a model of service delivery with clearly defined aims of keeping people with serious mental health problems in contact with services, reducing the extent of hospital admissions, and improving quality of life and social functioning of patients. ACT is delivered by a multidisciplinary team, in the community, often using the 'assertive outreach' principle of offering treatment assertively to uncooperative or reluctant patients. Team members share responsibility for each patient, and attempt to provide all the psychiatric and social care for them, rather than referring them on to other agencies. Staff to patient ratios is low. The intensive case management model (ICM) is a variant of the ACT meant for the most seriously ill patients. The evidence for the efficacy of the various types of case management models is variable because of differing definitions of the various models used and other methodological problems. Meta-analytic studies have concluded case management services to be either highly effective, or highly ineffective. However, consistent evidence suggests that, ACT, compared to standard care, is more likely to improve contact and satisfaction with services, decrease the use of hospital services, improve quality of life, as well as improve work and housing stability. This is especially so among patients who are high service users. The evidence regarding ICM is inconsistent with some reports findings gains similar to ACT, while others suggest that it is no better than ordinary case management (NICE, 2002; Stillo et al., 2001; Mueser et al., 1998; Ziguras et al., 2002).

COMMUNITY MENTAL HEALTH TEAMS

Community mental health teams are multidisciplinary teams that focus assessment and care away from hospital settings and offer a range of interventions tailored to the patient's specific needs. Despite the fact that community mental health teams remain the mainstay of community mental health care, there is surprisingly little evidence to show they are an effective way of organising services. One systematic review concluded that community mental health team management was superior to standard care in promoting treatment acceptance, reducing hospitalisations, and preventing suicide (Simmonds et al., 2001). However, the concept is perhaps still too ill defined to stand such examination (NICE, 2002).

CRISIS RESOLUTION TEAMS

Crisis resolution treatment teams are multidisciplinary teams that aim to avoid admitting acutely ill people to hospital by providing intensive home-based support, with a specific remit to deal with such situations, in and beyond 'office hours.' Controlled evidence shows that for people with schizophrenia and other serious mental health problems in an acute crisis, such teams are superior to standard hospital-based care in reducing admissions and shortening stay in hospital. They appear to be more acceptable than hospital-based care for acute crises, and are more successful in maintaining contact with patients. Crisis resolution teams may also have a marginally better effect on some clinical outcomes (NICE, 2002).

INDIAN RESEARCH

Antipsychotics Clinical trials

Tables 1 to 4 are an attempt to summarise results of Indian clinical trials with first and second-generation antipsychotics. It was not possible to include all studies because of considerations of space and unavailability of data. However, the studies included are a reasonable representation of the research in this area.
TABLE - 1  REPRESENTATIVE INDIAN TRIALS  
FIRST GENERATION ANTIPSYCHOTIC MEDICATIONS: SHORT-TERM TRIALS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Drug</th>
<th>Comparisons</th>
<th>Design</th>
<th>Op Dx</th>
<th>Std. Assmt</th>
<th>N</th>
<th>Duratn. (weeks)</th>
<th>Dose (mg/d)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kothari, 1962</td>
<td>Ftz (oral)</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>15</td>
<td>4</td>
<td>2.5-5</td>
<td>Poor response</td>
</tr>
<tr>
<td>Chatterjee &amp; Bhusan, 1963</td>
<td>Tdz</td>
<td>none</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>26</td>
<td>4-16</td>
<td>300</td>
<td>50% improved</td>
</tr>
<tr>
<td>Thomas &amp; Narayanan, 1965</td>
<td>Tfz</td>
<td>Unicpz</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>10</td>
<td>12</td>
<td>5-15</td>
<td>TFZ = Unicpz</td>
</tr>
<tr>
<td>Teja, 1967</td>
<td>Thiopro</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>Yes</td>
<td>25</td>
<td>6</td>
<td>15</td>
<td>56% improved</td>
</tr>
<tr>
<td>Mokashi &amp; Chandorkar, 1967</td>
<td>Thiopro (im)</td>
<td>Cpz, Placebo</td>
<td>DB, RCT</td>
<td>No</td>
<td>No</td>
<td>60</td>
<td>5 days</td>
<td>15</td>
<td>Thiopro &gt; Cpz</td>
</tr>
<tr>
<td>Menon &amp; Badsha, 1968</td>
<td>Tfz-thx</td>
<td>Tfz, Placebo</td>
<td>DB, RCT, Cross-over</td>
<td>No</td>
<td>Yes</td>
<td>30</td>
<td>16</td>
<td>15-30 (both drugs)</td>
<td>Thiothx &gt; Tfz</td>
</tr>
<tr>
<td>Kishore et al, 1970</td>
<td>Thiothx</td>
<td>Tfz, Thiopro, Procpz, Cpz, Triflpz</td>
<td>DB, RCT</td>
<td>No</td>
<td>Yes</td>
<td>60</td>
<td>12</td>
<td>10-30 (Thio-thx)</td>
<td>Procpz &gt; Thiothx &gt; Triflpz &gt; Thiopro &gt; Tfz &gt; Cpz</td>
</tr>
<tr>
<td>Bagadia et al, 1970</td>
<td>Cpz Tfz Flupen Triluo</td>
<td>ECT ICT</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>300</td>
<td>4</td>
<td>600-2400 Tfz-15-60 Triluo-2-6 Flupen-3-15</td>
<td>ECT &gt; Tfz, Cpz, Triluo &gt; Flupen &gt; ICT</td>
</tr>
<tr>
<td>Ramachandran &amp; Menon, 1972</td>
<td>Triluo</td>
<td>Placebo</td>
<td>DB, RCT</td>
<td>No</td>
<td>Yes</td>
<td>50</td>
<td>6</td>
<td>1.5</td>
<td>Triluo &gt; Placebo</td>
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Cont....
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<th>Comparisons</th>
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<th>Dose (mg/d)</th>
<th>Results</th>
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<tr>
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<td>Flupen</td>
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<td>Open</td>
<td>No</td>
<td>Yes</td>
<td>116</td>
<td>2-4</td>
<td>1.5-9</td>
<td>46.5% improved</td>
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<td>Triluo</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>Yes</td>
<td>76</td>
<td>4</td>
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<td>None</td>
<td>Open</td>
<td>No</td>
<td>Yes</td>
<td>53</td>
<td>4-10</td>
<td>2-6</td>
<td>45% improved</td>
</tr>
<tr>
<td>Kishore et al, 1972</td>
<td>Triluo</td>
<td>Thiotox, Procprz</td>
<td>DB, RCT</td>
<td>No</td>
<td>Yes</td>
<td>60</td>
<td>12</td>
<td>6 (Triluo)</td>
<td>All equal</td>
</tr>
<tr>
<td>Sharma &amp; Dutta, 1976</td>
<td>Pmz</td>
<td>Placebo</td>
<td>DB, RCT</td>
<td>No</td>
<td>Yes</td>
<td>34</td>
<td>4</td>
<td>1-5</td>
<td>Pmz &gt; placebo</td>
</tr>
<tr>
<td>Channabasavanna et al, 1976</td>
<td>Triluo</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>Yes</td>
<td>36</td>
<td>3</td>
<td>1.5</td>
<td>69% improved</td>
</tr>
<tr>
<td>Basu et al, 1996</td>
<td>Loxap</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>50</td>
<td>6</td>
<td>50-125</td>
<td>Loxapine effective</td>
</tr>
<tr>
<td>Emanuel et al, 1997</td>
<td>Loxap</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>66</td>
<td>6</td>
<td>50-150</td>
<td>Loxapine effective</td>
</tr>
</tbody>
</table>

* Other studies of loxapine are by Dube & Kumar, (1976); Seth et al., (1979)
### Table 2: Representative Indian Trials

**First Generation Antipsychotic Medications: Long-Term/Maintenance Trials**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Drug</th>
<th>Comparisons</th>
<th>Design</th>
<th>Op Dx</th>
<th>Std. Assmt</th>
<th>N</th>
<th>Duratn. (weeks)</th>
<th>Dose (mg/d)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al, 1965</td>
<td>Tbz</td>
<td>Insulin coma Rx (ICT)</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>306</td>
<td>1 year</td>
<td>15-60 mg/d</td>
<td>Tbz = ICT</td>
</tr>
<tr>
<td>Dube &amp; Mathur, 1966</td>
<td>Tbz</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>35</td>
<td>Few wks to months</td>
<td>100-300 mg/d</td>
<td>7.2% improved</td>
</tr>
<tr>
<td>Narayanan et al, 1967</td>
<td>Procpz</td>
<td>Cpz</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>20</td>
<td>20 weeks</td>
<td>100 mg/d (both drugs)</td>
<td>Procpz &gt; Cpz</td>
</tr>
<tr>
<td>Bagadia et al, 1973</td>
<td>Pmz</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>50</td>
<td>12 weeks</td>
<td>1-2 mg/d</td>
<td>88% benefited</td>
</tr>
<tr>
<td>Mahal &amp; Janakiramaiah, 1975</td>
<td>Pmz</td>
<td>Placebo</td>
<td>DB, RCT</td>
<td>No</td>
<td>Yes</td>
<td>62</td>
<td>6 months</td>
<td>2-4 mg/d</td>
<td>Pmz &gt; placebo</td>
</tr>
<tr>
<td>Bagadia et al, 1975</td>
<td>Pmz</td>
<td>Tbz</td>
<td>DB CT Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>50</td>
<td>6 months</td>
<td>Pmz - 2 mg/d Tbz-5 mg/d</td>
<td>Pmz = Tbz</td>
</tr>
<tr>
<td>Channabasavanna &amp; Michael, 1987</td>
<td>Penflu</td>
<td>Hpl, Placebo</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>12 weeks</td>
<td>20-60 mg/wk.</td>
<td>Penflu = Hpl &gt; placebo</td>
</tr>
<tr>
<td>Sharma, 1988</td>
<td>Penflu</td>
<td>Tbz</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>29</td>
<td>6 months</td>
<td>20-40 mg/wk.</td>
<td>Penflu &gt; Tbz</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Drug</td>
<td>Comparisons</td>
<td>Design</td>
<td>Op Dx</td>
<td>Std. Assmt</td>
<td>N</td>
<td>Duratn. (weeks)</td>
<td>Dose (mg/d)</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------</td>
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<td>-----------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Iyer et al, 1968</td>
<td>Flz ethanate</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>Yes</td>
<td>30</td>
<td>2 weeks</td>
<td>1.5-62.5 mg (single dose)</td>
<td>62.5% improved</td>
</tr>
<tr>
<td>Gehlot et al, 1977</td>
<td>Flz decanoate</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>30</td>
<td>20 weeks</td>
<td>25 mg/2-3 wks</td>
<td>60% improved</td>
</tr>
<tr>
<td>Bagadia et al,</td>
<td>Flz decanoate</td>
<td>None</td>
<td>Open, retrospective</td>
<td>No</td>
<td>Yes</td>
<td>83</td>
<td>4 months</td>
<td>6.25 mg/2 wks</td>
<td>Clinical, social, occupational improvement; high EPSE, 46% drop-outs</td>
</tr>
<tr>
<td>1979*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bagadia et al,</td>
<td>Piportil</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>27</td>
<td>4 weeks</td>
<td>50 mg/wk</td>
<td>76% improved</td>
</tr>
<tr>
<td>1979</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shukla, 1981</td>
<td>Flz decanoate</td>
<td>None</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>40</td>
<td>6 months</td>
<td>25 mg/3 wks</td>
<td>63% improved, 39% drop-outs</td>
</tr>
<tr>
<td>Verma &amp; Kulhara,</td>
<td>Hpl decanoate</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>4 weeks</td>
<td>50-300 mg/4 wks</td>
<td>Improvement in positive &amp; negative symptoms, few side effects</td>
</tr>
<tr>
<td>1989</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Drug</td>
<td>Comparisons</td>
<td>Design</td>
<td>Op</td>
<td>Dx</td>
<td>Std. Assmt.</td>
<td>N</td>
<td>Std. Assmt.</td>
<td>Duratn. (weeks)</td>
<td>Dose (mg/d)</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
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<td>-------------</td>
<td>---</td>
<td>-------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Zuclopen acetate</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>120</td>
<td>Yes</td>
<td>3 days</td>
<td>50 mg (2 doses)</td>
</tr>
<tr>
<td>Zuclopen decanoate</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>120</td>
<td>Yes</td>
<td>8 weeks</td>
<td>100-200 mg/2 wks</td>
</tr>
</tbody>
</table>

* Other trials with fluphenazine ethanate by Shah et al., (1971) & Bagadia et al., (1972) found it effective.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Drug</th>
<th>Comparisons</th>
<th>Design</th>
<th>Op Dx</th>
<th>Std. Assmt</th>
<th>N</th>
<th>Duratn. (weeks)</th>
<th>Dose (mg/d)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma &amp; Bhardwaj, 1997</td>
<td>Risp</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>25</td>
<td>8</td>
<td>4-10</td>
<td>Efficacious in positive &amp; negative symptoms</td>
</tr>
<tr>
<td>Agarwal et al, 1997</td>
<td>Cloz</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes (Treatment Resistant)</td>
<td>Yes</td>
<td>29</td>
<td>16</td>
<td>50-450 Effect by 9-16 weeks, no leucopenia</td>
</tr>
<tr>
<td>Agarwal et al, 1998</td>
<td>Risp</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>165</td>
<td>6</td>
<td>6-8</td>
<td>Efficacious in positive &amp; negative symptoms, EPSEs in 40%</td>
</tr>
<tr>
<td>Agashe et al., 1999</td>
<td>Risp</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>24</td>
<td>6-8</td>
<td>Risp safe, effective, mild side effects</td>
</tr>
<tr>
<td>Bajaj et al., 1999</td>
<td>Risp</td>
<td>None</td>
<td>Open</td>
<td>Yes (moderately refractory)</td>
<td>Yes</td>
<td>30</td>
<td>&gt; 2 years</td>
<td>2-10</td>
<td>Improvement in negative symptoms 25% re-emergence of positive symptoms</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Drug</td>
<td>Design</td>
<td>Op Dx</td>
<td>N</td>
<td>Std Assmt</td>
<td>Duratn (weeks)</td>
<td>Dose (mg/d)</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>------</td>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Desai et al., 1999</td>
<td>Cloz</td>
<td>Open</td>
<td>Yes</td>
<td>28</td>
<td>Yes</td>
<td>12</td>
<td>241 (mean)</td>
<td>Significant improvement, no neutropenia</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 1999</td>
<td>Centb</td>
<td>DBRCT</td>
<td>Yes</td>
<td>44</td>
<td>Yes</td>
<td>6</td>
<td>Centb-1.5-4.5</td>
<td>Hpl-5-15</td>
<td></td>
</tr>
<tr>
<td>Srivastava &amp; Gopa, 2000</td>
<td>Risp</td>
<td>Open</td>
<td>Yes</td>
<td>50</td>
<td>Yes</td>
<td>1 year</td>
<td>Risp-2</td>
<td>Hpl-5-15, Risp &gt; Hpl on symptoms, Risp &gt; Hpl on social measures, suicidality, readmission</td>
<td></td>
</tr>
</tbody>
</table>

Dose: Cloz = 241 (mean), Centb = 1.5-4.5, Hpl = 5-15, Risp = 2
TABLE - 4 REPRESENTATIVE INDIAN TRIALS
(CONTINUED) SECOND GENERATION ANTIPSYCHOTIC MEDICATIONS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Drug</th>
<th>Comparisons</th>
<th>Design</th>
<th>Op Dx</th>
<th>Std. Assmt</th>
<th>N</th>
<th>Duratn. (weeks)</th>
<th>Dose (mg/d)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srivastava et al., 2001</td>
<td>Risp</td>
<td>None</td>
<td>Post-marketing survey</td>
<td>-</td>
<td>-</td>
<td>67</td>
<td>-</td>
<td>-</td>
<td>3-4 mg/d effective &amp; preferred</td>
</tr>
<tr>
<td>Suresh Kumar et al., 2001</td>
<td>Risp</td>
<td>None</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>24</td>
<td>12</td>
<td>6-8</td>
<td>Improvement in positive, negative &amp; depressive symptoms, high rates of EPSEs</td>
</tr>
<tr>
<td>Agarwal &amp; Chadda, 2001</td>
<td>Risp</td>
<td>OD vs. BD dose</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>44</td>
<td>8</td>
<td>4-8</td>
<td>79-82% response, OD = BD dose</td>
</tr>
<tr>
<td>Avasthi et al., 2001</td>
<td>Olanz</td>
<td>Hpl</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>27</td>
<td>12</td>
<td>5-20</td>
<td>Improvement in positive, negative &amp; depressive symptoms</td>
</tr>
<tr>
<td>Chandra et al., 2002</td>
<td>Centb</td>
<td>Risp</td>
<td>DB RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>44</td>
<td>8</td>
<td>Centb-3-4.5 Risp-4-6</td>
<td>Centb = Risp</td>
</tr>
</tbody>
</table>
Abbreviations: Op Dx- operationalized diagnosis using standard criteria; Std. assmt - structured assessments using reliable measures; Duratn/Duration - duration of trial; DB RCT- double-blind randomised controlled trial; N- number of patients; Fz- fluphenazine; Tdz-thioridazine; Tfz-trifluoperazine; Unicz-uniclorpromazine; ICT-insulin coma therapy Thiothx-thiothexene; Procicz-prochlorpromazine; Triflz-triluzopromazine; Flupentixol; Pmz-pimozide; Loxap-loxapine; Penflu-penfluperidol; Hpl-haloperidol; Zuclopentixol; Risp-risperidone; Cloz-clozapine; Centb-centbutindole; Olanz-olanzapine; CBZ-carbamazepine

FGAMS

Clinical trials of first-generation medications began in the 1960s in India, and since then a large number of drugs have been examined for their effectiveness in indigenous patient populations. Almost every aspect of treatment with FGAMs including acute (short-term) treatment, maintenance (long-term) treatment, and treatment with depot injections has been assessed.

Drugs have been compared with placebo, with each other, with ECT, and even with insulin coma therapy. All, but one trial has found the different FGAMs to be effective and well tolerated. Drugs have consistently proved to be better than placebos, better than insulin coma therapy, and more or less comparable to ECT. Minor differences in efficacy between two drugs have been reported in some studies, but overall no drug has been shown to be clearly superior to others. Efficacy in the long-term, and efficacy as well as safety of depot preparations have also been demonstrated.

Therefore, these findings are broadly similar to what has been reported in Western patient populations. However, several methodological limitations make it difficult to interpret the results of these drug trials. Randomised controlled trials are few. Many studies have not used standardized diagnoses, and/or structured assessments to rate change. Samples have often been too small and heterogeneous. Follow-up periods have sometimes been inadequate. Nevertheless, there is no doubt that these drugs are safe and efficacious under Indian conditions.

SGAMS

Trials involving SGAMs are understandably fewer and have begun appearing only in the past few years. Methodology is variable, but the number of RCTs is still low. These drugs have been shown to be effective against positive, negative and depressive symptoms, as well as other parameters e.g. functioning, readmission etc. Efficacy has been demonstrated in short-term, and (less often) in long-term treatment of schizophrenia. SGAMs are generally well tolerated. Of particular interest is the drug centbutindole, which has been developed indigenously. It appears to have an atypical profile, and efficacy is comparable to other second-generation drugs.

ADJUNCTIVE MEDICATIONS

Studies of adjunctive medications in the treatment of schizophrenia are included in table-5. The number of trials is too few to make any reasonable conclusions about the usefulness of these agents.
### TABLE - 5 REPRESENTATIVE INDIAN TRIALS

**ADJUNCTIVE MEDICATIONS IN THE TREATMENT OF SCHIZOPHRENIA**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Comparison(s)</th>
<th>Design</th>
<th>Diagnoses</th>
<th>No.</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dube et al., 1981</td>
<td>Lithium vs. Cpz, placebo</td>
<td>DB RCT crossover</td>
<td>ICD 9</td>
<td>60</td>
<td>4 weeks</td>
<td>Lithium reduced overactivity, excitement, hostility, withdrawal</td>
</tr>
<tr>
<td>Raju, 1984</td>
<td>CBZ &amp; CBZ + antipsychotics</td>
<td>Open</td>
<td>RDC (unresponsive to FGAMs)</td>
<td>9</td>
<td>variable</td>
<td>7 improved</td>
</tr>
<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dua et al., 1990</td>
<td>Imipramine 75 mg + Cpz 800 mg vs. Cpz + placebo</td>
<td>DB RCT</td>
<td>RDC</td>
<td>18</td>
<td>6 weeks</td>
<td>Adjunctive imipramine - no benefit</td>
</tr>
<tr>
<td>Agarwal &amp; Agarwal, 2000</td>
<td>Fluoxetine up to 80 mg + antipsychotics</td>
<td>Open</td>
<td>DSM IV comorbid OCD</td>
<td>7</td>
<td>12 weeks</td>
<td>5 showed improvement in OC symptoms</td>
</tr>
<tr>
<td><strong>ANTICHOLINERGICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behere &amp; Ramakrishna, 1983</td>
<td>Anticholinergics + Antipsychotics vs. Antipsychotics alone</td>
<td>Open</td>
<td>Psychosis mainly schizophrenia</td>
<td>70</td>
<td>4 weeks</td>
<td>No difference in EPSEs between both groups</td>
</tr>
<tr>
<td><strong>L-DOPA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sethi et al., 1990</td>
<td>L-dopa</td>
<td>Open</td>
<td>Schizophrenia with TD</td>
<td>30</td>
<td>14 weeks</td>
<td>80% showed &gt; 50% reduction in TD</td>
</tr>
</tbody>
</table>

**Abbreviations:** CBZ- carbamazepine; Cpz= chlorpromazine; DB RCT- double-blind randomised controlled trials
OTHER DRUG TRIALS

Trials have also been carried out with other drugs including experimental compounds, ayurvedic preparations, and drugs such as propanolol or naloxone.

ISSUES RELATING TO DOSE

It is widely believed that there are ethnic differences in pharmacokinetic characteristics of psychotropic drugs. Studies suggest that Asian patients often need lower doses of antipsychotics than non-Asian patients. Asian patients also tend to have higher serum levels with equivalent doses of antipsychotics, though this might not be true for all antipsychotic medications (Kuruvilla, 1996). The immediate implications for practicing clinicians are that relying on Western guidelines for dose requirements may not be appropriate for Indian patients. Beyond this, the evidence is too meagre and conflicting to serve as a guide to suit the requirements of our patients. Clinical experience suggests that the doses should be lower than recommended in standard (Western) texts. At the same time the doses used in drug trials have been within the range used in Western patients, and the drugs still seem to be well tolerated. Then again, in the case of some drugs such as risperidone, the need for lower doses has been recognized (Basu et al., 2000; Suresh Kumar et al., 2001).

SIDE EFFECTS

Clinical experience and pharmacokinetic data suggest that Indian patients should be more sensitive to side effects. However, the few studies (table-6) that specifically address this issue have only been able to find a marginally higher prevalence of side effects such as EPSEs. Data from drug trials yield higher rates, but could be biased because they rely heavily on high potency FGAMs. Further studies are needed to either confirm or refute clinical suspicions.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ray et al., 1992</td>
<td>25 inpatients, 14 with RDC schizophrenia, exposed to Hpl, Tiz, Ffz, structured ratings for akathisia</td>
<td>28% had akathisia few patients complained</td>
</tr>
<tr>
<td>Dutta et al., 1994</td>
<td>Structured assessments for TD in 350 patients on antipsychotics for 3 months</td>
<td>25.5% had persistent TD, higher age, higher total doses, longer duration of treatment correlated with TD</td>
</tr>
<tr>
<td>Suresh Kumar &amp; Manoj Kumar, 1997</td>
<td>Retrospective comparison of 42 patients with DSMIIIR schizophrenia vs. 42 patients with mood disorders</td>
<td>EPSEs - dystonia-17%; parkinsonism-60%; akathisia-30% TD-6.7%</td>
</tr>
<tr>
<td>Basu et al., 2000</td>
<td>Retrospective review of 43 patients, predominantly schizophrenia, on risperidone, mean dose 6.26 mg/d</td>
<td>67.4% had EPSEs, most patients developed EPSEs at doses of 5-7 mg/d</td>
</tr>
<tr>
<td>Chopra &amp; Raghuram, 2001</td>
<td>Retrospective review of 13 cases of NMS, treated with bromocriptine or amantadine</td>
<td>Re-challenge with high potency drugs led to partial recurrence; treatment with single agent better</td>
</tr>
<tr>
<td>Gupta et al., 2003</td>
<td>Prospective 4-year study, 15 cases of NMS</td>
<td>Risk factors - male sex, new exposure, parenteral drugs, rapid dose increases, combination of antipsychotics, concomitant lithium, agitation, dehydration, infections</td>
</tr>
</tbody>
</table>

Abbreviations: Tfz-trifluoperazine, Ffz-fluphenazine, Hpl-haloperidol.
PLASMA-LEVELS

Determination of plasma levels is only recommended for inexplicable non-response or side effects. However, for reasons of cost, cultural differences, doubtful utility of and lack of facilities for such tests, therapeutic drug monitoring has been discouraged (Kala, 1997).

COST OF TREATMENT/AVAILABILITY

Although the situation has changed, not all antipsychotic preparations are available in India. The acquisition costs of some FGAMs (e.g. trifluoperazine) are lower than SGAMs (Indian Drugs Review, 2003). Then again, studies have also shown that the costs of SGAMs are more or less similar to FGAMs in India (Girish et al., 1999). In general, there is a lack of comprehensive Indian data on cost effectiveness of antipsychotic drugs. Cost of illness studies have shown that drugs constitute a much higher proportion of total costs of treatment, compared to Western data. Further, even if drugs are available they might be out of reach of the average patient. The prohibitive costs of some drugs can deter patients from complying with treatment. Hospitals may supply one or two preparations, but the supply is often unreliable.

MONITORING

Monitoring for response, side effects and compliance are essential components of drug treatment. Several professionals are often involved in this process, especially during the maintenance phase when such monitoring may have to be done in the community. The lack of such facilities in India means that standards requirements for drug delivery and monitoring are not met. Practices have to be modified, and family members are often relied upon to fill this gap.

CULTURAL BELIEFS

There is also growing awareness that cultural beliefs might affect drug compliance by influencing attitudes to taking drugs, expectations from drug treatment, and the labelling or reporting of therapeutic/adverse events. Beliefs of patients and their families about causes of illness determine several key issues such as treatment seeking, expectations from treatment, adherence to treatment etc. Belief in supernatural causes is common and families have a lot of faith in traditional methods of treatment. Allopathic drugs are considered too strong, believed to produce excessive 'heat', and in general be detrimental to health. Certain side effects can be especially distressing for some e.g. amenorrhoea for young unmarried women, or sexual dysfunction for men. Expectations of quick relief often clash with the long duration of treatment needed. Families often expect clinicians to take all decisions themselves. An awareness of socio-cultural factors is thus essential for effective pharmacotherapy (Kuruvilla, 1996).

ECT

ECT though not favoured in the West for treating schizophrenia is often used in India for this purpose. Table- 7 lists the Indian studies that have focused on the role of ECT in the treatment of schizophrenia. The evidence, particularly for acute efficacy of ECT is quite impressive. The consistent finding across several studies is that the combination of ECT and antipsychotics is superior to antipsychotics alone. It leads to a much faster resolution of symptoms during the first few weeks of treatment. However, some studies suggest that this advantage is lost if adequate doses of comparator antipsychotics are used. Further, almost all studies show that the enhanced efficacy only persists for the first few weeks following which ECT and antipsychotics have similar effects. Reviews of the subject have also that ECT has an edge over antipsychotics in the early part of treatment, which disappears after 8-12 weeks. Predictors of good response include acute onset, shorter duration of illness, stable premorbid adjustment, and the presence of psychotic, catatonic or affective symptoms. ECT is not useful in chronic schizophrenia, in those with negative symptoms and in relapse prevention. Some authors have proposed that there are other advantages of ECT that make it a useful treatment option in developing settings. These include low costs of treatment, the relative lack of long-term side effects, the need for lower doses of antipsychotics when used with ECT, and the shortened duration of hospital stay that results from rapid recovery. However, there is a lot of stigma among patients and relatives regarding ECT, although studies about patient acceptance are equivocal in this regard (Goswami et al., 2003). Such negative attitudes are often not helped by the varying standards in the delivery of this treatment, across different settings.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Design</th>
<th>Comparison(s)</th>
<th>Op. Dx</th>
<th>Std. Assmt.</th>
<th>N</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah &amp; Bagadia, 1962</td>
<td>Prospective, open</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>398</td>
<td>3 years</td>
<td>Best results in those ill for &lt; 6 months</td>
</tr>
<tr>
<td>Dutta-Ray &amp; Kapoor, 1963</td>
<td>Open</td>
<td>ECT vs. Cpz</td>
<td>No</td>
<td>No</td>
<td>200</td>
<td>1 year</td>
<td>Best results in acute onset illness of &lt; 1 year</td>
</tr>
<tr>
<td>Bagadia et al., 1970</td>
<td>Open</td>
<td>ICT, Cpz, Trifluc, Flupen</td>
<td>No</td>
<td>No</td>
<td>300</td>
<td>4 weeks</td>
<td>ECT &gt; drugs &gt; ICT</td>
</tr>
<tr>
<td>Desmukh et al., 1980</td>
<td>Open</td>
<td>Daily vs. 3 ECTs/week</td>
<td>No</td>
<td>Yes</td>
<td>60</td>
<td>3 weeks</td>
<td>Daily = 3 ECTs per week</td>
</tr>
<tr>
<td>Janakiramiah &amp; Subbakrishna, 1981</td>
<td>Single-blind RCT</td>
<td>ECT + Cpz vs. Cpz alone</td>
<td>Yes</td>
<td>Yes</td>
<td>44</td>
<td>6 weeks</td>
<td>ECT &gt; Cpz by wk 2; ECT = Cpz by wk 6</td>
</tr>
<tr>
<td>Janakiramiah et al., 1982</td>
<td>Single-blind RCT</td>
<td>Cpz 300 mg vs. Cpz 300 mg + ECT vs. Cpz 500 mg vs. Cpz 500 mg + ECT</td>
<td>Yes</td>
<td>Yes</td>
<td>60</td>
<td>6 weeks</td>
<td>ECT faster, augments low, not high dose Cpz</td>
</tr>
<tr>
<td>Bagadia et al., 1983</td>
<td>DB RCT</td>
<td>Real ECT + placebo vs. Simulated ECT + Cpz</td>
<td>Yes</td>
<td>Yes</td>
<td>38</td>
<td>3 weeks</td>
<td>ECT = Cpz</td>
</tr>
<tr>
<td>Natani et al., 1983</td>
<td>RCT</td>
<td>ECT vs. Hpl 15 mg vs. ECT + Hpl 15 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>90</td>
<td>3 weeks</td>
<td>Wks 1 &amp; 2 ECT +Hpl best; Wk 3 all equal</td>
</tr>
<tr>
<td>Agarwal &amp; Winny, 1985</td>
<td>DB RCT</td>
<td>Cpz 800-1200 mg + real ECT vs. Cpz + simulated ECT</td>
<td>Yes</td>
<td>Yes</td>
<td>28</td>
<td>4 weeks</td>
<td>Both conditions equal</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Design</td>
<td>Comparison(s)</td>
<td>Op. Dx</td>
<td>Std. Assmt.</td>
<td>N</td>
<td>Duration</td>
<td>Results</td>
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<tr>
<td>Abraham &amp; Kulhara, 1987</td>
<td>DB RCT</td>
<td>Tfz 20 mg + real ECT vs. Tfz + simulated ECT</td>
<td>Yes</td>
<td>Yes</td>
<td>22</td>
<td>26 weeks</td>
<td>Up to 8 weeks real ECT superior; 12 &amp; 26 weeks both groups same</td>
</tr>
<tr>
<td>Sarkar et al., 1994</td>
<td>DB RCT</td>
<td>Hpl 15 mg + true ECT vs. Hpl + sham ECT</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>6 months</td>
<td>Both groups equal</td>
</tr>
<tr>
<td>Goswami et al., 2003</td>
<td>DB RCT of treatment resistant patients</td>
<td>Cpz 1000 mg + real ECT vs. Cpz + sham ECT</td>
<td>Yes</td>
<td>Yes</td>
<td>25</td>
<td>4 weeks</td>
<td>True ECT &gt; Sham ECT</td>
</tr>
</tbody>
</table>

**Abbreviations:** Op Dx- operationalized diagnosis using standard criteria; Std. Assmt - structured assessments using reliable measures; Duration - duration of trial; DB RCT- double-blind randomized controlled trial; N- number of patients; Tfz- trifluoperazine; ICT- insulin coma therapy; Cpz- chlorpromazine; Thiothx- Thiothene; Trifluo- trifluoperidol; Flupen- flupenthixol; Hpl- haloperidol
PSYCHOSOCIAL INTERVENTIONS

There are major differences in the mental health services and the socio-cultural milieu between developing and developed countries. There is a glaring lack of infrastructure, funds and political support for mental health care in developing countries. This is compounded by a severe shortage of adequately trained and motivated staff. Services are mostly urban-based and therefore relatively inaccessible for a majority of patients who reside in rural areas. In such a situation families have become caregivers of the first and last resort. Cultural beliefs, norms and attitudes to mental illness, as well as expectations from treatment also differ greatly. Given these fundamental differences psychosocial treatments often used so successfully in the West, cannot be directly transposed to developing settings. Instead it has been proposed that these countries need to develop their own theory of rehabilitation and test models of intervention based on this theory (Philips & Pearson, 1994). Although some progress has been made, tables 8 a, b and c indicate that this area still remains relatively neglected in India. There seems to be adequate amount of research on psychosocial aspects such as family burden and distress, coping styles of patients and carers, role of life events and social support, disability, quality of life, work performance, rehabilitation needs etc. However, interventions studies are sorely lacking (John, 1997).

FAMILY TREATMENT (TABLE 8A):

In India there has been a long tradition of involving families in the treatment of mentally ill relatives. However, few efforts had been made to develop structured programmes suited to the cultural context, and still fewer efforts to test them. Pioneering work with the families of mentally ill patients was done by Dr. Vidyasagar in Amritsar. Family wards exist in hospitals like CMC, Vellore and NIMHANS, Bangalore, and involvement of families in patient care is a routine practice in many other centres. However, the hospital-based, and resource-intensive and infrastructure-dependent nature of such programmes means that they might not be the most appropriate models to adopt (Shankar & Menon, 1993). Of late there have been efforts to develop a framework for family interventions suitable for both community and institution-based treatment. Sadly, there are no controlled studies of family interventions from India.

**TABLE-8A REPRESENTATIVE INDIAN TRIALS**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Description</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narayanan et al., 1972</td>
<td>Descriptive study of treatment in a family ward</td>
<td>104 patients, 76 with schizophrenia</td>
<td>&quot;gratifying results&quot; with family treatment</td>
</tr>
<tr>
<td>Chacko et al., 1967</td>
<td>Descriptive study of treatment in a family ward</td>
<td>Mixed group; mainly with schizophrenia</td>
<td>Benefits from family treatment</td>
</tr>
<tr>
<td>Verghese et al., 1986</td>
<td>Assessment of knowledge &amp; attitudes of carers</td>
<td>94 caregivers attending a family participation programme</td>
<td>Positive change in knowledge &amp; attitudes following attendance</td>
</tr>
<tr>
<td>Shankar &amp; Menon, 1993</td>
<td>Description of a family intervention module</td>
<td>Case reports</td>
<td>Intervention useful</td>
</tr>
<tr>
<td>Sovani, 1993</td>
<td>Descriptive study of a one-day family-psycho educational programme</td>
<td>Caregivers</td>
<td>Caregivers expressed need for such programmes</td>
</tr>
</tbody>
</table>
Home-care (Table-8b): Efforts to develop and study an alternative to hospital-based care, particularly those by Pai and her colleagues, were reasonably successful, but have not been followed-up. Some studies have also indicated the useful role community psychiatric nurses can play (Murthy et al., 1997; John, 1997).

**TABLE-8B REPRESENTATIVE INDIAN TRIALS**

**PSYCHOSOCIAL THERAPIES: HOME TREATMENT**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Description</th>
<th>Sample/Assessments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suman et al., 1980</td>
<td>Descriptive study of an intervention consisting of home visits, counselling &amp; social casework</td>
<td>30 patients with psychosis</td>
<td>Interventions beneficial</td>
</tr>
<tr>
<td>Pai &amp; Kapur, 1982; 1983</td>
<td>Home treatment by trained nurse vs. hospital treatment</td>
<td>54 patients with ICD 9 diagnosis of schizophrenia, first episodes assessed for symptoms, social functioning, family burden</td>
<td>After 6 months home treatment group significantly improved on symptoms, functioning, family burden</td>
</tr>
<tr>
<td>Pai &amp; Roberts, 1983</td>
<td>Home treatment by trained nurse vs. hospital treatment</td>
<td>37 patients with ICD 9 diagnosis of schizophrenia, first episodes assessed for symptoms, social functioning, family burden</td>
<td>At 2 year follow-up home treatment group significantly improved on symptoms only, hospitalised less often</td>
</tr>
<tr>
<td>Pai et al., 1985</td>
<td>Home treatment by trained nurse vs. hospital treatment</td>
<td>25 chronically mentally ill patients with schizophrenia, psychosis, epilepsy with &gt; 2 years illness assessed for symptoms, social functioning, family burden</td>
<td>At 2-year follow-up home treatment group less likely to have been hospitalised; no difference on symptoms, functioning, family burden</td>
</tr>
</tbody>
</table>
REHABILITATION:

Culture-specific characteristics that rehabilitation programmes need to adopt in order to be successful in developing country settings have been mentioned (Gopinath & Rao, 1994). These include:

- shifting the locus of care from the hospital to the community
- focusing primarily on families of patients, supporting them, helping them cope and easing their burden
- developing a network of services from the periphery to the centre
- placing a particular emphasis on vocational rehabilitation, given the centrality of work in these cultures
- adopting techniques which are culturally based and, hence, more acceptable
- mobilising both private and public resources
- motivating and training more number of mental health professionals

However, apart from the studies mentioned in table 8c, and a handful of reports on the utility of industrial and occupational therapy, there is limited Indian research in this area (Sarada Menon et al., 1985). Moreover, setting up of rehabilitation services and facilities as envisaged by the National Mental Health Plan (Ministry of Health and Family Welfare, Govt. of India, 1982) has never achieved fruition (Murthy et al., 1997; John, 1997).

TABLE–8C REPRESENTATIVE INDIAN TRIALS
PSYCHOSOCIAL THERAPIES: OTHER INTERVENTIONS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Description</th>
<th>Sample/Assessments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thara &amp; Srinivasan, 1998</td>
<td>Intervention package including psychoeducation, social skills training, occupational therapy &amp; medication management vs. antipsychotic medications alone; open trial of 1-year</td>
<td>135 patients with DSMIIIIR schizophrenia assessed for negative symptoms, disability, psychological impairments</td>
<td>Both treatment groups improved, only minor differences between both</td>
</tr>
<tr>
<td>Chatterjee et al, 2003</td>
<td>Community-based rehabilitation (CBR) vs. outpatient care; longitudinal trial of 1 year</td>
<td>207 patients with chronic schizophrenia as per ICD 10; assessed for symptoms and disability</td>
<td>CBR better in reducing disability, improving outcome and treatment-adherence</td>
</tr>
</tbody>
</table>