SPECIAL SITUATIONS

TREATMENT-RESISTANCE/DIFFICULT TO TREAT PATIENTS

Although the introduction of antipsychotic medication was the first specific treatment proven to be efficacious, a sizeable number of individuals receiving these drugs failed to respond adequately. Treatment-resistant schizophrenia is relatively common, in that between a fifth and a third of patients show a disappointing response to adequate trials of first-generation antipsychotic drugs (NICE, 2002).

The pharmacological treatment options for treatment-resistance include increasing the dose of the antipsychotic or decreasing the dose if poor treatment adherence is the result of adverse drug. Switching to another class of FGAMs is another option though the evidence for the possible value of such a strategy is inconsistent. The use of adjunctive medications such as mood stabilizers, antidepressants or benzodiazepines has also been considered, but the role of such drugs is probably limited. With the advent of clozapine it has been proposed that its unusual mode of action may be of value for those with treatment-resistance. Other second-generation drugs have also been suggested as possible alternatives in the treatment of refractory patients (Morrison, 1996; APA, 1997; NICE, 2002; Koshino, 1999; Miller et al., 1999).

Most of the research in this area shows that clozapine has superior efficacy when compared with first-generation antipsychotics in situations of treatment-resistance (Wahlbeck et al., 1999; Chakos et al., 2001). However, some recent evidence seems to indicate otherwise, and that differences from other SGAMs may only be modest. For example a meta-analysis of 5 controlled comparisons of risperidone with clozapine in treatment-resistance concluded that it was not clear whether or not the two drugs were equally effective, or whether one was actually superior (NICE, 2002; Tuunainen et al., 2002; Moncrieff, 2003).

There are several definitions of treatment-resistance from the very strict to less restrictive ones. A consensus definition proposes that schizophrenia be considered treatment-resistant when there is a lack of a satisfactory clinical improvement despite the sequential use at least of two antipsychotics, one of which is a SGAM, at recommended doses for a minimum of 6 to 8 weeks. This definition reflects a broadening of the group of individuals who were viewed as clinically eligible for treatment with clozapine (APA, 1997; NICE, 2002).

The first step in the management of treatment-resistance is to establish that the disorder has failed to respond to adequate trials of first-generation antipsychotic drugs in terms of dosage, duration and adherence. Other causes of non-response should be considered such as, non-compliance, adverse effects, comorbid conditions such as substance misuse, before actually diagnosing treatment refractoriness.

If the symptoms of schizophrenia are unresponsive to FGAMs, a trial of a second-generation agent such as risperidone or olanzapine may be considered prior to making a diagnosis of treatment-resistant schizophrenia and a trial of clozapine is initiated.

In individuals with clear evidence of treatment-resistance clozapine should be introduced at the earliest opportunity. Clozapine should be gradually titrated to effective doses.

There is growing evidence that monitoring plasma clozapine concentration may be helpful in establishing the optimum dose of clozapine in terms of risk-benefit ratio particularly for patients showing a poor therapeutic response and/or significant side effects despite appropriate dosage. However, there is considerable disagreement regarding the critical levels. Routine monitoring is thus not recommended. Response to clozapine is comparatively slow and an adequate trial should be of 3-6 months. Monitoring for side effects (especially leucopenia/agranulocytosis) needs to be maintained, although there is some variability in the recommended parameters of such monitoring (Morrison, 1996; APA, 1997; NICE, 2002; Koshino, 1999; Miller et al., 1999).

The role of ECT in such situations has not been examined, although one Indian study suggests it could be useful (Goswami et al., 2003). Psychosocial interventions such as cognitive therapy, family treatment, assertive outreach or crisis intervention are also beneficial in refractory or difficult to treat patients.

Treatment options in patients unresponsive to clozapine are limited, but could include addition of antipsychotics, antidepressants, mood stabilizers, ECT and psychosocial treatments (Barnes et al., 1996; Williams et al., 2002).

DEPRESSION

Despite differing definitions of the term a substantial rate of depression has consistently been found in patients of schizophrenia. Available reports indicate that the modal rate of depression in schizophrenia is around 25%; the prevalence of depressive symptoms may be higher. Depression appears to occur during all phases of schizophrenia with the period 6-12 months after resolution of acute psychotic symptoms (post-psychotic phase) being a particular period of risk. Post-psychotic depression is also associated with a higher risk of suicide.

A rational approach to treating depression in schizophrenia first needs to consider and rule out possible differential diagnoses for the condition. These include organic conditions, negative symptoms, antipsychotic associated side effects (dysphoria, akinesia and akathisia), schizoaffective depression, stress-related reactions, and an impending psychotic episode.

Controlled trials with SGAMs have shown that they are superior to first-generation antipsychotics in their antidepressant efficacy. In addition clozapine may be particularly effective in patients at high risk for suicide. Therefore switching to a second-generation drug followed by minimization of EPSEs and optimisation of treatment with FGAMs are the initial options in treating depression during the acute psychotic phase. Antidepressants are generally ineffective during the acute phase. They may even worsen the psychosis, and are best avoided. On the other hand, results of controlled trials have demonstrated the efficacy of adjunctive antidepressant therapy in post-psychotic depression. Although the data mainly concerns addition of tricyclic drugs to FGAMs, a few studies of specific serotonergic reuptake inhibitors and SGAMs have found this combination to be effective as well. Thus, a trial of antidepressants in patients with post-psychotic depression may be a worthwhile strategy. The evidence for the usefulness of other treatments such as lithium, valproate or carbamazepine is limited (Levinson et al., 1999; Siris, 2000). Clinical experiences suggest ECT may be helpful.

FIRST-EPISODE PSYCHOSIS AND EARLY INTERVENTION

The early phase of psychosis including a period of untreated psychosis is a critical period with regard to the future course of the illness. Studies of first-episode of psychotic disorders including schizophrenia show that the average time from onset of psychotic symptoms to initiation of treatment is often a year or more. Longer durations of untreated psychosis are powerful predictors of subsequent poor outcome. The evidence from such studies also suggests that when deterioration occurs, it does so in the first 2-3 years of the illness. Moreover, research evidence also indicates that comprehensive programmes of drug and psychosocial interventions with adults who show early signs of psychosis may contribute to a lowered incidence of major episodes of schizophrenia. Field trials of early intervention strategies also demonstrate that they are effective and can be routinely applied in clinical situations (Birchwood et al., 1998; Falloon et al., 1998). Critics of this approach while agreeing on the need for early intervention argue that there are substantial ethical, practical and economic problems in implementing such strategies (Pelosi/Birchwood, 2003). Nevertheless, there appears to be some consensus regarding general principles of treatment of first-episode psychosis or first-episode schizophrenia (Birchwood et al., 2001).

The aims of such treatment are to reduce the duration of untreated psychosis, to promote remission

through effective pharmacological and psychosocial interventions, to maximize functioning, and to prevent relapse and other adverse outcomes. Early detection, comprehensive assessment, emphasis on continued engagement, and flexible treatment enable early intervention services to meet these goals. Recommendations for pharmacotherapy include a short antipsychotic-free observation period to determine diagnosis, use of SGAMs as first-line treatments to achieve remission, and early assessment and intervention in situations of treatment resistance. Controlled trials have demonstrated the efficacy of several second-generation antipsychotics in the treatment of first-episode psychosis. Though they are not unequivocally superior to FGAMs in such patients, they are preferred because of their better side-effect profile. Trials of antipsychotics have also underlined the necessity for using low doses of drugs while treating patients with first episodes of psychosis. Doses as low as 2-3 mg/day of haloperidol or 2-4 mg/day of risperidone have shown to be the optimal in treating positive symptoms without inducing too many side effects. It is still not clear for how long patients with first-episode psychosis should continue maintenance antipsychotic medication. A 1-2 year period is usually recommended (APA, 19997; 2004), though many patients may require longer periods, and some shorter periods of treatment than this (Johnson, 1985; Gitlin et al., 2001).

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