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opinion & debate

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First-line atypical antipsychotics for schizophrenia are appropriate – with psychosocial interventions†

Conventional antipsychotics and traditional services

Conventional antipsychotics, historically the mainstay of schizophrenia treatment, were ineffective in many patients, at least 30% fitting treatment-resistance criteria (Kane & Lieberman, 1987). All had the same mechanism of action: none was any more effective in the individual than any other. Therapeutic nihilism accepted poorly controlled positive symptoms and disabling negative symptoms: nearly all patients suffered side-effects (Barnes & Edwards, 1993), particularly extrapyramidal side-effects (EPS) and hyperprolactinaemia. Conventional antipsychotics raise prolactin to a range associated with sexual dysfunction or even macroprolactinoma: effects in men include erectile dysfunction and hypospermatogenesis; in women, galactorrhoea, oligo- or amenorrhoea, hirsutism and increased risk of osteoporosis. In both men and women there is loss of libido, and a link between hyperprolactinaemia and weight gain.

Historically, measures with no evidence base, such as polypharmacy and high doses of antipsychotic, were frequently implemented. Even recently, our local audit found 28% of patients were prescribed more than one antipsychotic simultaneously: high dose guidelines were not followed.

Over 60% of patients are non-compliant in the community, with 40–65% of out-patients stopping their regular medication within 6 weeks of starting it (Johnson, 1988). Most relapses are caused by inadequate compliance (Davis *et al*, 1994): side-effects are a major contributor. Depots represent a partial answer, but cause more side-effects than oral treatment. Unfortunately, in schizophrenia each relapse tends to leave behind an increasing burden of unresolved symptoms (Lieberman, 1996).

Historically services centred on staff and facilities, not patients and families – whose satisfaction with services was not an issue. Leaving aside that quality of life may approximate to satisfaction with services in chronic disorder, satisfaction cannot but affect compliance and therefore the efficacy of treatment (Awad, 1995). Locally, relatives expressed considerable dissatisfaction with lack of information about, and lack of involvement in, patient care.

New treatments: atypical antipsychotics and psychosocial interventions

A classic randomised controlled trial (RCT) (Kane *et al*, 1988) comparing the atypical antipsychotic clozapine to chlorpromazine in treatment-resistant patients should have destroyed forever the twin notions that neuroleptics did not work unless they caused EPS and that poor outcomes were immutable. Despite an almost complete lack of EPS, after 6 weeks of clozapine treatment 30% of patients compared to 3% of chlorpromazine treated patients met clinical criteria for significant improvement.

All studies demonstrate that the EPS profile of atypical drugs is far milder than that of conventional drugs. Most, notably olanzapine and quetiapine, do not cause hyperprolactinaemia.

Numerous studies suggest that atypicals are superior to conventionals for positive and negative symptoms (Leucht *et al*, 1999; Stahl, 1999): compliance may be improved. In addition, the novel mechanisms of action of the atypicals afford them the potential for cognitive remediation, with its important implications for improving personal function (Green, 1996): there is accruing evidence that this potential is translated into reality (Harvey & Keefe, 1998). Schizophrenia is really no different from any other chronic medical condition: at disease onset the diagnosis must be made promptly and effective treatment begun. Medication is necessary but insufficient: a therapeutic alliance allows the patient to participate actively in his or her treatment and own responsibility for it. Information about the illness, the medication, monitoring of health, accessing services etc. is required. Patients need help to accept the limitations imposed by illness, and families need to solve the kinds of problems that arise when a member is ill, especially a young person on the verge of adulthood and independence. To provide this input, the service must back up medication management with appropriate psychosocial interventions (PSI). It has been demonstrated that family work reduces relapse rates in schizophrenia, while cognitive–behavioural therapy is useful in coping with positive symptoms.

Atypicals first-line drug

At least 15% of drug naïve patients have Parkinsonian symptoms already: with special equipment, symptoms can be detected in nearly 40% (Caliguiri *et al*, 1993). First-episode patients are extremely sensitive to the motor effects of conventional drugs, yet nearly all first-episode patients treated early and effectively do very well indeed (Lieberman, 1996). The superior tolerability of atypicals should obviate treatment cessation because of side-effects, which launches the majority of patients on a relapsing career of deterioration: at most, 15% of patients recovering from a first episode of schizophrenia remain well, but nobody can tell who they are. Duration of remission is immaterial to relapse rate on cessation,

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which is 15% of survivors every month (Davis *et al*, 1994). Very low dose regimes, 'drug holidays' and treatment targeted to imminent relapses are not feasible and cannot be recommended. Low dose haloperidol is as poorly tolerated as ordinary therapeutic doses, but is ineffective as an antipsychotic (Zimbroff *et al*, 1997). Even low/moderate, flexible doses of conventional drugs in outpatients result in a significant burden of EPS associated with residual psychopathology difficult to distinguish from independent disease symptoms (Berardi *et al*, 2000). So why not establish the first-episode patient on the best tolerated, most effective treatment available – in other words, an atypical antipsychotic – and keep him or her on it indefinitely? (Lieberman, 1996).

Even patients with severe disabilities may benefit. A local psychiatric ward with expected turnover of one patient per year discharged 33 patients in 3 years: patients became accessible to rehabilitation on atypical drugs. Impression from practice is that nearly all patients between the first episode and the chronic state make worthwhile improvements. Even if this is no more than reducing the burden of side-effects, it should no longer be acceptable to impose this burden on patients.

Barriers to progress

Drug treatment comprises less than 5% of the direct costs of schizophrenia, but is easily identified as a target for costcutting. Notwithstanding the volume of research evidence that atypical antipsychotics are at worst cost-neutral and at best cost-effective, our local prescribing committee took a decision to restrict the initial prescription of atypical antipsychotics to consultants, despite their unanimous opposition.

Such actions are supported by an influential review (Adams & NHS Centre for Reviews and Dissemination, 1999), whose conclusions include: "All statements of the effects of atypical antipsychotics must be qualified . . . atypical antipsychotics are expensive . . ." It completely ignores the neuroscience that underpins novel mechanisms of action and dismisses extensive trial evidence regarding efficacy, tolerability and cost, despite nearly all of it pointing in the same direction. Traditional symptom outcome measures are rejected as difficult to interpret for health professionals: leaving aside that health professionals ought to be familiar with the symptoms of the illnesses they encounter, to widen the target beyond the symptoms that these drugs are designed to control is asking for trouble because bias from factors independent of drug treatment will inevitably be introduced. Trials are further criticised for their attrition rates and recruitment of unusual patients, yet more double-blinded randomised studies are called for. This highly restrictive methodology is inevitably associated with substantial sample restriction and drop out, simply because it is inimical to real life practice.

Using atypicals properly

There is a very big issue around using atypical drugs properly, in other words backed up by appropriate psychosocial interventions. There is no point in handing out a prescription without assessing the psychosocial problems of the patient and family, or implementing and monitoring PSI solutions. This is, of course, what happens in traditional services (and clinical trial protocols). Such practice will inevitably minimise the drug's apparent benefits.

Extensive research on treatment delay confirms its association with poor outcomes. An ideal service would aim to improve outcomes by instituting early effective treatment, combining an atypical antipsychotic with PSI. It might even identify high risk groups, for instance children of people with schizophrenia, detected the prodromal syndrome and reduce the duration of untreated psychosis (Philips *et al*, 1999). Such a service might improve the prospects of patients even more radically than the introduction of chlorpromazine in the 1950s did.

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