Quetiapine: a well-tolerated and effective atypical antipsychotic

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Quetiapine is an atypical antipsychotic, licensed in the UK for the treatment of schizophrenia. This review of published literature identifies the evidence that quetiapine is both effective and well-tolerated and highlights the particular indications in which quetiapine will be of most value to clinicians and patients.

Schizophrenia is a common and serious mental disorder with a lifetime morbid risk of approximately 1% (Jablensky, 1995) and a prevalence of approximately 0.7% (Kessler et al, 1994). The clinical picture is variable but symptoms can include those of reality distortion (e.g. hallucinations and delusions), psychomotor poverty, disorganization and affective disturbance. As a chronic and disabling illness, there are considerable and far-reaching health-economic implications. While the 'direct' costs of treatment, e.g. medication and inpatient treatment, are substantial, these are far outweighed by 'indirect' costs, e.g. lost productivity. Lynch et al (2001) estimated the total annual cost of schizophrenia in the UK as being up to £1.7 billion.

Non-compliance is a major problem in schizophrenia and contributes both to relapse and poor outcome. Even with antipsychotic treatment, many patients continue to experience symptoms; moreover, burdensome side effects are a common experience. Some patients with schizophrenia are unable to function independently and require specialist care; suicide rates among schizophrenic individuals are disturbingly high, with 10–13% ending their lives in this way (Caldwell and Gottesman, 1990). Unfortunately, for many patients, standard antipsychotic treatments prove ineffective or intolerable. Clinicians need therefore to remain abreast of new drug treatments.

CONVENTIONAL TREATMENTS

Conventional antipsychotic agents differ from each other more in their side effects than in their therapeutic effects, which are broadly comparable. Conventional antipsychotics all occupy dopamine D2 receptors and as a result, cause extrapyramidal symptoms (EPS), even at relatively low doses. Typical antipsychotics are commonly associated with various side effects, which are often distressing, disabling and persistent. Patients suffering from severe side effects may not comply with their drug treatment, increasing the likelihood of relapse and hospitalization (Van Putten and May, 1978; Awad et al, 1996).

Although EPS are the major side effects with conventional treatment regimens, patients commonly experience other side effects, e.g. hyperprolactinaemia, sexual dysfunction, anticholinergic effects (constipation and blurred vision), sedation, cardiovascular problems and weight gain.

NEW OPPORTUNITIES OFFERED BY THE ATYPICAL ANTIPSYCHOTICS

Clozapine, the first atypical antipsychotic, is associated with low D2 occupancy and does not cause EPS. Its use, however, has been restricted to patients with proven resistance or intolerance to other agents, because of the association with agranulocytosis (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2002). Over recent years, three newer atypical antipsychotics have become available in routine clinical practice: risperidone, olanzapine and quetiapine. Compared with standard agents, the atypical drugs are more effective against both positive and negative symptoms (Hellewell and Gerlach, 2000). They are also all associated with a lower risk of EPS, tardive dyskinesia and hyperprolactinaemia than standard agents (Hellewell and Gerlach, 2000; Kasper and Müller-Spahn, 2000).

There are clear differences in pharmacology between the various agents; clinical experience accords with this and suggests significant differences in receptor interactions and side-effect profiles. For example, while dose-related EPS are seen with olanzapine and risperidone (Hellewell and Gerlach, 2000), EPS are essentially absent with quetiapine across the full dose range. Data also suggest that risperidone and possibly olanzap-

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ine cause some dose-related hyperprolactinaemia (Hamner and Arana, 1998), whereas quetiapine tends not to cause hyperprolactinaemia, irrespective of dose (Hellewell and Gerlach, 2000).

This article reviews the published data on efficacy and side effects of quetiapine, focussing particularly on issues of most interest to the clinician treating schizophrenia and other psychoses.

QUETIAPINE

Pharmacology

Quetiapine (Seroquel, AstraZeneca, London), a dibenzothiazepine, is an atypical antipsychotic. Like clozapine, quetiapine binds to a number of neurotransmitter receptors (Goldstein, 1996) and has a greater affinity for serotonin 5-HT_2 receptors than for dopamine D2 receptors, together with considerable activity at histamine receptors and α-adrenoceptors (Goldstein, 1996). Quetiapine is administered twice daily, with maintenance doses for adult patients of 400–700 mg/day, although lower doses are often sufficient in patients with hepatic impairment and the elderly.

EFFICACY

The antipsychotic efficacy of quetiapine was established in three placebo-controlled studies in acute schizophrenia (Borison et al, 1996; Arvanitis and Miller, 1997; Small et al, 1997). In each of these studies, quetiapine produced a statistically greater improvement in psychopathology than placebo. Additional examination of global function measures, response rates and positive symptom scores confirmed these results and provided further reassurance to the clinician of the intrinsic antipsychotic efficacy of quetiapine.

Negative symptoms were also significantly improved by quetiapine in each of the three studies (Borison et al, 1996; Arvanitis and Miller, 1997; Small et al, 1997). Kasper and Müller-Spahn (2000) reviewed the improvements in negative symptoms reported in acute studies with quetiapine, risperidone and olanzapine and concluded that these are very similar. Thus, the effect of quetiapine on negative symptoms in acute schizophrenia is greater than placebo and comparable with that of other atypical antipsychotics.

Comparative studies

Peuskens and Link (1997) compared quetiapine with chlorpromazine in acute schizophrenia and showed that quetiapine achieved a statistically and clinically significant greater response rate (65% *vs* 52%, P=0.04). Kasper and Müller-Spahn (2000) reported a meta-analysis of studies of haloperidol in acute schizophrenia and schizoaffective disorder. A significantly higher proportion of patients responded to quetiapine than haloperidol, suggesting a greater efficacy for the atypical agent. A substantial open study comparing quetiapine and risperidone over 4 months' treatment indicated that the two agents may be equally effective in the treatment of schizophrenia, although quetiapine produced less EPS than did risperidone (Tandon et al, 2001).

There have been no studies in which patients have been randomized either to quetiapine or olanzapine, so direct comparisons are not possible. However, Kasper and Müller-Spahn (2000) showed very similar response rates to the two agents once adjusted for placebo response rate.

To summarize, it appears that quetiapine is more effective than the conventional antipsychotics haloperidol and chlorpromazine. While randomized blinded comparative studies are not yet available, quetiapine is likely to be at least as effective in the treatment of acute schizophrenia as both risperidone and olanzapine.

Efficacy in partial responders and the treatment resistant

Up to 20% of patients with schizophrenia fail to respond fully to conventional treatments (Van Putten and May, 1978; Awad et al, 1996). These patients, described as 'partial responders', pose considerable treatment difficulties. In a double-blind, randomized trial, Emsley et al (2000) showed that quetiapine may have particular efficacy in these patients. Schizophrenic patients were first treated for 4 weeks with fluphenazine; those showing an incomplete response were randomized to quetiapine or haloperidol. After 8 weeks' treatment, the response rate was significantly greater with quetiapine than with haloperidol, suggesting that quetiapine may offer particular benefit to the clinician when treating partial responders.

TOLERABILITY

Quetiapine appears to be well tolerated. This is illustrated by the observation that adverse events occurred at a similar rate in both quetiapine and placebo-treated patients, as did discontinuation because of adverse events, in the clinical trial programme (Kasper and Müller-Spahn, 2000). In contrast, discontinuation occurred at twice the rate on both haloperidol and chlorpromazine as on quetiapine (Kasper and Müller-Spahn, 2000). Data indicate that quetiapine continues to be well tolerated in the long term (Hellewell et al, 1999).

Low incidence of EPS

The occurrence of EPS in the quetiapine clinical trial programme was assessed using rating scales, reports of side effects and use of anticholinergic

medication. A consistent conclusion is that quetiapine is associated with no more EPS than placebo, across the entire dose range. In the placebo-controlled studies as a whole, fewer than 9% of patients receiving quetiapine were prescribed anticholinergic medication, compared with over 12% of patients allocated to placebo. Quetiapine-treated patients reported no more EPS than did patients on placebo, even at the highest doses (Kasper and Müller-Spahn, 2000).

Comparison with other antipsychotics

This freedom from EPS across the full dose range differs from the patterns seen with some of the other atypical antipsychotics. In particular, there is evidence of dose-related increases in EPS with both olanzapine and risperidone (reviewed by Hellewell and Gerlach, 2000).

Comparative studies between quetiapine and haloperidol confirm a lower burden of EPS in quetiapine-treated patients. For example, in Arvanitis and Miller's (1997) study, only 12% of quetiapine-treated patients received anticholinergic medication, compared with 48% of the haloperidol-treated patients.

Implications for use in vulnerable groups and long-term treatment

Quetiapine has been studied in a number of groups, such as the elderly, adolescents and those with Parkinson's disease or dementia of the Lewy body type, who may, in practice, be particularly vulnerable to developing EPS. These studies, reviewed by Kasper and Müller-Spahn (2000), show that quetiapine has a low likelihood of inducing EPS, even in these vulnerable patients. This may offer further reassurance of quetiapine's benign EPS profile and utility in patients with schizophrenia more commonly encountered in routine clinical practice.

Tardive dyskinesia is often a complication of long-term treatment with conventional antipsychotics, often proving disfiguring and irreversible. As the atypical agents are associated with a lower level of acute EPS, this has led to optimism that there will be a lower incidence of tardive dyskinesia in longer term treatment. Preliminary studies indicate that quetiapine appears to be associated with a lower risk of tardive dyskinesia in both adult and elderly patients than would be expected with conventional antipsychotics (Kasper and Müller-Spahn, 2000).

Neutral in effects on prolactin and weight

Hyperprolactinaemia is a common side effect of the conventional antipsychotics and may lead to gynaecomastia, menstrual dysfunction, impotence and, in the long term, osteoporosis. The side effects are distressing and frequently lead to discontinuation of treatment. Unlike most other atypicals, quetiapine does not appear to cause sustained elevations in plasma prolactin; many patients receiving quetiapine in the clinical trial programme showed a normalization of previously elevated levels. Clear differences were seen between quetiapine and the conventional antipsychotics, chlorpromazine and haloperidol, in terms of effects on prolactin. Arvanitis and Miller (1997) also showed that quetiapine was indistinguishable from placebo in its effect on plasma prolactin across the full dose range.

Weight gain with antipsychotic treatment has come into focus of late, as substantial weight gain has been seen with both olanzapine and clozapine (Kasper and Müller-Spahn, 2000). As well as its effects on physical wellbeing, weight gain is often a source of patient dissatisfaction and can contribute to non-compliance. Quetiapine, however, appears to exert little effect on weight (Kasper and Müller-Spahn, 2000). Brecher et al (2000) showed that the mean weight gain over 1 year's treatment with quetiapine was 1.53 kg, and analysis of weight change by dose showed no evidence of dose-related weight changes.

Patients' subjective evaluations of quetiapine treatment

The good general tolerability profile of quetiapine and, in particular, its low propensity to cause hyperprolactinaemia and EPS, suggest that quetiapine may be associated with greater acceptability to patients than alternative treatments. Hellewell et al (1999) surveyed the subjective experiences of a group of 129 patients, who had each been receiving quetiapine in open label treatment for at least 6 months. Patient satisfaction with quetiapine was excellent. Reported side effects over the preceding month were uncommon, with 97.7% of the sample reporting mild side effects or none at all. Significantly, no patients appeared to have experienced EPS. These and other positive evaluations were reflected in a high proportion (96.6%) of respondents indicating a readiness to continue quetiapine treatment (Hellewell et al, 1999).

FUTURE DIRECTIONS

Quetiapine is a well-tolerated and effective atypical antipsychotic, with a place as a first-line treatment for schizophrenia and potentially other psychotic disorders. A health economic evaluation has indicated that quetiapine may be associated with a significant cost saving, as a result of reduced inpatient treatment costs (Lynch et al,

2001). In view of its benign EPS profile, quetiapine is likely to have a particular place in the treatment of patients vulnerable to developing EPS, such as the elderly, those with bipolar disorders and patients early in their course of illness. A series of studies are now underway in patients with dementia and bipolar disorders, in order to examine these issues more fully.

CONCLUSIONS

Quetiapine is an effective and well-tolerated atypical antipsychotic. Meta-analysis of the comparative studies in acute schizophrenia have indicated that quetiapine is more effective than conventional treatments such as haloperidol (Kasper and Müller-Spahn, 2000). In addition, a study carried out in a patient group with a history of partial response to conventional treatments indicated that quetiapine may be particularly effective in this population (Emsley et al, 2000). A study comparing risperidone and quetiapine indicated that quetiapine may be equally effective, yet produces less EPS (Tandon et al, 2001). In general, quetiapine is well tolerated (Hellewell et al, 1999). Both EPS and prolactin elevation occur no more commonly with quetiapine than with placebo (Arvanitis and Miller, 1997). Effects on the QT interval do not appear to be a particular concern with quetiapine (for a full review, see Dev and Raniwalla, 2000). In addition, quetiapine is neutral in its effect on weight (Brecher et al, 2000). Thus, quetiapine deserves serious consideration as a first-line antipsychotic treatment. Dosing is flexible, a reasonable dose for an adult patient with schizophrenia is 200 mg morning and night; this allows flexibility for the clinician to increase dosing up to the daily maximum dose of 750 mg. HM

Conflict of interest: Dr Hellewell has accepted fees for lectures, consultancy and participation in advisory boards, grants to enable the completion of research projects and sponsorship to attend scientific meetings from the manufacturers of quetiapine and of other products mentioned in this article.

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KEY POINTS

- Quetiapine is an effective and well-tolerated atypical antipsychotic.
- Clinical trials have demonstrated that quetiapine is superior in efficacy to the conventional antipsychotics, chlorpromazine and haloperidol; quetiapine also appears to be of equivalent efficacy to olanzapine and risperidone.
- Quetiapine has proven utility in patients with a history of partial response to antipsychotic treatment.
- Even at the highest doses, quetiapine is associated with no increases in plasma prolactin or extrapyramidal symptoms; freedom from extrapyramidal symptoms is also seen in patients vulnerable to developing extrapyramidal symptoms, such as the elderly and those with organic disorders.
- Over periods of up to 1 year, and irrespective of dose, quetiapine appears neutral in its effect on weight.
- Surveys of patients' subjective experiences with long-term quetiapine treatment indicate few side effects and high levels of satisfaction and tolerability.
- Quetiapine deserves consideration as a first-line treatment for patients with schizophrenia and other psychoses.