REVIEW ARTICLE

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Quetiapine

A Review of Its Safety in the Management of Schizophrenia

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Abstract

Quetiapine, a dibenzothiazepine derivative, is a atypical antipsychotic which has greater *in vitro* binding affinity for serotonin 5-HT_2 receptors than for dopamine D_2 receptors. Quetiapine effectively treats both the positive and the negative symptoms of schizophrenia and is also associated with an incidence of ex-

trapyramidal symptoms no greater than placebo across the entire dose range. In addition, it does not cause persistent hyperprolactinaemia.

Quetiapine is associated with high levels of patient acceptability and satisfaction, which may result from its combination of efficacy and relatively benign adverse effect profile. The drug is well tolerated and has a low propensity to cause adverse events both during acute and long term treatment in the adult populations. The adverse effect profile of quetiapine makes the drug advantageous for patient populations who are susceptible to the adverse effects of drugs. Indeed, preliminary data show quetiapine to be very well tolerated in the elderly. Overdoses of quetiapine of up to 20g have been reported; however, with appropriate management in an intensive care setting there have been no reported fatalities. Quetiapine is metabolised by the cytochrome P450 3A4 isoenzyme, and the dose may need to be adjusted if quetiapine is co-administered with drugs which affect the activity of this isoenzyme. Overall, quetiapine has a favourable risk-benefit profile that should make it a valuable first-line agent in the treatment of schizophrenia.

Quetiapine is an atypical antipsychotic, and is a dibenzothiazepine derivative with greater *in vitro* binding affinity for serotonin 5-HT_{2A} receptors than for dopamine D_2 receptors.[1,2] This property is widely considered to predict atypicality, which is defined clinically as minimal or absent extrapyramidal symptoms (EPS) at clinically relevant doses.

Clinical trials in over 3700 patients have consistently shown quetiapine to be effective and well tolerated in the treatment of schizophrenia. Two 6-week randomised, double-blind, placebo-controlled trials in moderately to severely ill patients with schizophrenia[3,4] demonstrated the efficacy of quetiapine compared with placebo in the treatment of both the positive and negative symptoms of schizophrenia. Comparative trials have shown quetiapine to be at least as effective as chlorpromazine,[5] haloperidol[3,6-8] and risperidone[9] in treating the symptoms of schizophrenia, with quetiapine having a tolerability profile superior to each of the comparators.[3,5-9]

Conventional and other atypical antipsychotic drugs produce a range of adverse effects, of which EPS are some of the most problematic. Other adverse effects encountered with these agents include sexual dysfunction (frequently as a consequence of hyperprolactinaemia), potent anticholinergic effects, cardiovascular effects, epileptic seizures, severe blood dyscrasias and bodyweight gain.[10] It has been suggested that some of these effects, in particular EPS, may compromise compliance[11,12] and also lead to suicide in patients with schizophrenia.[13,14] Quetiapine has been shown to have a benign adverse effect profile, with a very low incidence of EPS, no persistent increases in serum prolactin level and high patient acceptability.[15,16] Quetiapine's favourable benefit-risk ratio may be particularly advantageous in patient populations vulnerable to experiencing adverse effects, such as the elderly and those in poor general health.

This article reviews the safety data available on quetiapine. Where appropriate, the adverse event profile and frequency of adverse events for quetiapine are compared with those of both conventional and atypical antipsychotics. The relationship of adverse effects to the pharmacological profile of quetiapine is also discussed.

1. Pharmacological Mechanisms of Adverse Reactions

Quetiapine interacts with a broad range of neurotransmitter receptors. It has high α_1-adrenoceptor antagonist activity (IC_{50} = 94 nmol/L), moderate antagonist activity at histamine receptors (IC_{50} = 30 nmol/L), lower D_2 and 5-HT_2 receptor antagonism (IC_{50} = 329 and 148 nmol/L, respectively), and minimal antagonist activity at D_1 receptors

Table I. Proposed pharmacological mechanisms for the adverse effects of quetiapine

Neurotransmitter	Receptor/pharmacological effect	Clinical adverse effects	Occurrence and attribution[a]
Dopamine	D_2 antagonism	Parkinsonian symptoms	-
		Dystonia	-
		Akathasia	-
		Tardive dyskinesia	-
		Increase in prolactin levels	-
Serotonin	5-HT antagonism	Bodyweight gain	+
Acetylcholine	Muscarinic antagonism	Constipation	+
		Dry mouth	+
Norepinephrine (noradrenaline)	α_1, α_2 and β antagonism	Sedation	+
		Hypotension	+
Histamine	H_1 antagonism	Sedation	+

a Pharmacological properties that are believed to cause the clinical adverse effects of quetiapine.

+ = effects that have been observed; **-** = adverse effects that might be caused by a particular pharmacological effect but are not seen (to a significant extent) with quetiapine.

(IC_{50} = 1268 nmol/L).[17,18] The proposed pharmacological mechanisms for adverse effects associated with quetiapine are shown in table I.

2. Frequency of Adverse Reactions

Overall, quetiapine is very well tolerated in patients with schizophrenia. In phase II and III clinical trials, adverse events were based on patient reports. The most frequently reported adverse events with quetiapine versus placebo were somnolence (21.9 *vs* 10.7%), headache (13.4 *vs* 17.5%) and dizziness (9.9 *vs* 4.4%).[19] The dose of quetiapine should be titrated to an initial target dosage of 400 mg/day over 4 to 5 days to minimise orthostatic hypotension.[19] Patients in poor health are generally more vulnerable to developing adverse effects when treated with antipsychotic therapy.[20] Most of the reported adverse events were mild or moderate in severity. Overall, the discontinuation rate attributable to adverse events for patients receiving quetiapine was similar to that for placebo recipients (5 *vs* 3%).[19]

3. Adverse Reactions Profile by Body System

3.1 Central Nervous System

3.1.1 Extrapyramidal Symptoms and Tardive Dyskinesia

It is widely accepted that noncompliance with antipsychotic drugs is commonly due to EPS.[11,20] In 1 survey, 46% of patients with schizophrenia took less antipsychotic drug than the amount prescribed. This reluctance to comply with treatment was significantly associated with EPS.[11] In the long term, EPS can lead to the development of tardive dyskinesia. Patients over 65 years of age are 5 times more likely to develop tardive dyskinesia than patients less than 40 years old.[19] A study by Jeste et al.[21] found that, using the Schooler-Kane criteria, 26% of elderly patients developed tardive dyskinesia related to treatment with conventional antipsychotics by the end of 1 year, 52% by the end of 2 years, and 60% by the end of 3 years. The low propensity of quetiapine to induce EPS is a considerable clinical advantage over other antipsychotics.[22]

Most conventional antipsychotics and some atypical antipsychotics have marked effects on the nigrostriatal dopaminergic systems, resulting in EPS-related adverse effects. However, biochemical and neurophysiological studies indicate that quetiapine acts preferentially on mesolimbic and amygdaloid rather than nigrostriatal dopaminergic systems.[3] This selectivity of quetiapine suggests it will be associated with a lower risk of EPS, and an even lower risk of tardive dyskinesia, than that associated with antipsychotics. This theory is supported by the results of preclinical studies.[17,22-24]

Clinical trial data showed that quetiapine over a dosage range of 75 to 750 mg/day was associated with an overall incidence of EPS similar to that

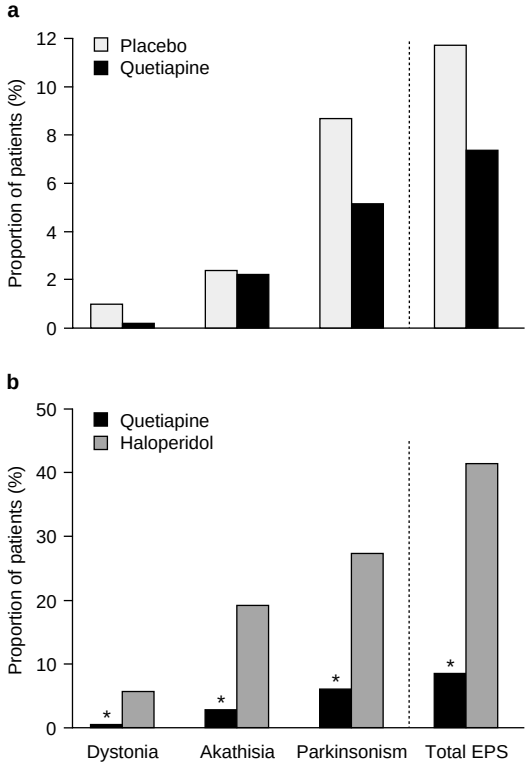

Fig. 1. Proportion of patients developing acute extrapyramidal symptoms (EPS), and EPS-related dystonia, akathisia and parkinsonism while receiving either: (**a**) quetiapine (n = 2953) or placebo (n = 206) in placebo-controlled, randomised, clinical trials of 6 to 8 weeks' duration; or (**b**) quetiapine (n = 479) or haloperidol (n = 279) in comparator studies in the quetiapine clinical trial programme. Patients may have experienced more than 1 EPS-related adverse effect. * $p < 0.01$ *vs* haloperidol.[19]

reported with placebo (8.8 *vs* 11.7%, respectively) as measured by changes in the Simpson-Angus Scale,[3,4] the Abnormal Involuntary Movement Scale,[3,4] and the Barnes Akathisia Scale.[4] These data are illustrated in figure 1a, which indicates that, for every category of acute EPS, patients were no more likely to develop EPS while receiving quetiapine than when receiving placebo.[3,4] In these studies, only 8.6% of patients receiving quetiapine required anticholinergic medication for EPS, compared with 12.6% of those receiving placebo.[3] Moreover, in a study in which patients receiving fluphenazine were switched to either quetiapine or haloperidol, the proportion of patients requiring anticholinergic medication decreased in those switched to quetiapine, but increased in those receiving haloperidol.[7]

Figure 1b shows the proportions of patients recorded as developing acute EPS in the haloperidol-controlled studies.[3,8] The method of measurement of EPS was not reported; however, EPS were reported as an adverse event in over 40% of patients receiving haloperidol, compared with only 8% of patients treated with quetiapine. Furthermore, significantly more patients receiving haloperidol developed each of the acute EPS-related adverse events of dystonia, akathisia and parkinsonism.[3,4]

The incidence of EPS observed with a drug is a predictor of its ability to cause tardive dyskinesia.[25] Current clinical evidence shows that the incidence of EPS with quetiapine is low, and as a con-sequence the risk of tardive dyskinesia should also be low. Pharmacologically, this may be explained by the 5-HT_2 receptor activity of quetiapine ameliorating the drug's D_2 receptor-mediated effects (the latter of which may independently induce dyskinesia). An analysis of 1447 patients treated with quetiapine in phase III clinical trials indicated that the incidence of tardive dyskinesia (assessed using the Glazer-Morgenstern and Schooler-Kane criteria) might be lower than that reported with conventional antipsychotics in other studies.[22] Indeed, in elderly patients, who are more likely to develop tardive dyskinesia, the incidence of persistent tardive dyskinesia was lower with quetiapine (2.7% after 1 year) than with conventional antipsychotics (overall incidence 5% after 1 year).[26]

3.1.2 Sedation

Sedation is observed with a number of antipsychotic drugs and can be particularly useful in managing the aggressive patient. Indeed, in clinical trials with quetiapine, somnolence was the most frequently reported adverse effect.[19] The frequency of somnolence with quetiapine (21.6%) is similar to that reported for chlorpromazine (17.8%).[19] This adverse effect may be explained pharmacologically

by the high affinity of quetiapine for histamine H_1 receptors.[17]

Although sedation is clinically useful in the short term, persistent somnolence is not. With quetiapine, this somnolence typically occurs during the first 2 weeks of treatment, disappearing with continued treatment, thus obviating any need for dose reductions.[19]

3.1.3 Seizures

Quetiapine is associated with a low incidence of seizures. In the clinical trial programme of 3700 patients, the occurrence of epileptic seizures in patients treated with quetiapine was no greater than that observed in patients receiving placebo.[19] In phase II/III clinical trials the incidence of convulsions with quetiapine and placebo was 0.2 and 0.5%, respectively.[19] However, despite the low risk of seizures with quetiapine, the drug should be administered with caution to patients who have a history of seizures.

3.2 Autonomic Nervous System

3.2.1 Temperature Regulation

In phase II/III clinical trials, an increase in body temperature has been reported in 1.1% of patients receiving quetiapine, compared with 1.0% of those receiving placebo.[19] However, any such incidents still require the exclusion of neuroleptic malignant syndrome (NMS) as a possible cause.

3.2.2 Neuroleptic Malignant Syndrome

NMS is a rare and potentially fatal idiosyncratic dose-independent adverse drug reaction. It is associated with a sudden loss of body temperature control during drug therapy, resulting in a rise in body temperature that can be fatal (within 24 to 72 hours) due to consequent renal and respiratory failure. Although the pathogenesis is unknown, NMS may be related to hypodopaminergic function. All antipsychotic drugs have been associated with possible NMS with half of all reports involving haloperidol.[27] Hence, NMS is a class label for all currently available antipsychotics. The incidence of NMS anticipated with antipsychotic use is approximately 0.5%.[28] However, in clinical trials with quetiapine, the incidence of possible NMS was considerably lower (0.09%).[19] As of 31 December 1999, postmarketing surveillance data indicate that 24 cases of NMS have been reported after 109 000 to 164 000 patient-years quetiapine exposure. In the unlikely event that a patient should develop NMS whilst receiving quetiapine, the drug should be withdrawn immediately and the patient should receive appropriate therapeutic interventions and close monitoring.

3.2.3 Tachycardia

Tachycardia is an anticipated adverse effect of many antipsychotic drugs and is related to the fall in blood pressure induced by antagonism at α_1-adrenoceptors. Tachycardia may also be related to the anticholinergic properties of a number of these agents. In a placebo-controlled trial, quetiapine was associated with an increase in heart rate of 7 beats/min, compared with a mean increase of 1 beat/min with placebo.[29] This tachycardia may be a reflex response to the hypotension that occurs in some patients. It appears to be mainly limited to the initial dose titration period and seldom leads to cessation of treatment.

3.3 Cardiovascular System

3.3.1 Blood Pressure

The α_1-adrenoceptor antagonist activity of quetiapine, as with a number of other antipsychotics, may result in the development of orthostatic hypotension, which may in turn precipitate falls. The elderly are the most susceptible patient population with regard to the adverse effects of orthostatic hypotension.[30,31] If quetiapine induces orthostatic hypotension, particularly during the initial dose-titration period, more gradual titration should be considered. It is advisable that patients experiencing orthostatic hypotension during therapy with quetiapine should rise slowly from sitting or prone positions. Most patients treated with quetiapine who experience hypotension do not require pharmacological intervention. In the event that treatment-related hypotension persists, increased hydration and elastic support stockings may be helpful in managing the condition. Postmarketing surveillance data

indicate that, as of 31 December 1999, there were 14 cases of orthostatic hypotension and 36 cases of hypotension (including the 14 of orthostatic hypotension) reported in 109 000 to 164 000 patient-years quetiapine exposure.[19]

3.3.2 QT Changes

In clinical trials, quetiapine was associated with a small mean decrease in QTc (Fridericia correction). However, QTc prolongation was also reported for a small number of patients. None of these changes were associated with any clinical sequelae.[19]

3.3.3 Sudden Death

Sudden deaths have occurred (at a rate of 1.5 to 2%)[32] during treatment with antipsychotic drugs, usually in younger patients. These deaths usually occur within an hour or so of the onset of symptoms; no pre-existing pathology is known and post-mortem findings fail to elucidate the cause of death. However, many are presumed to result from ventricular arrhythmias.

A total of 12 deaths (0.4%), none of which were sudden, were reported during phase II/III clinical trials in 2953 patients receiving quetiapine.[19] Post-marketing surveillance data indicate that as of 31 December 1999, 100 patients were either known to be taking quetiapine at the time of death or had taken quetiapine within 30 days of death. In the vast majority of cases, the reporter assessed the death as unrelated to quetiapine. Sudden unexplained deaths (as defined by the Royal College of Psychiatrists and the American Psychiatric Association)[33] represent 1 of the 100 (1.0%) deaths reported during or within 30 days of quetiapine treatment in 109 000 to 164 000 patient-years exposure (based on a maintenance dosage of 300 to 450 mg/day). From this evidence, there is no causal relationship between the use of quetiapine and sudden unexplained death.

3.4 Gastrointestinal System

Quetiapine has minimal effects on the gastrointestinal system. In placebo-controlled phase II/III clinical trials the most frequently reported gastrointestinal adverse events with quetiapine were constipation (7.2 *vs* 4.9% for placebo), dry mouth (8.0 *vs* 2.9% for placebo), dyspepsia (4.2 *vs* 2.4% for placebo), nausea (4.6 *vs* 4.9% for placebo) and vomiting (4.3 *vs* 5.3% for placebo).[19] Nausea and vomiting may be the result of dopamine and/or 5-HT receptor stimulation. Constipation can be treated symptomatically using stool softeners, laxatives, fibre supplements and adequate fluid intake.

3.5 Hepatic System

Typical antipsychotic drugs have a mild effect on liver function enzymes. Quetiapine's effects, however, are minimal. Consequently, routine liver monitoring is not required during treatment with quetiapine. Asymptomatic, transient and reversible elevations in serum transaminase levels (primarily alanine aminotransferase) were observed in some patients receiving quetiapine in clinical trials, usually during the first 3 weeks of treatment.[19] In placebo-controlled trials, 6% of patients receiving quetiapine had elevations greater than 3 times the upper limit of the normal reference range (compared with 1% of patients receiving placebo); these levels readily returned to pretrial values with continued quetiapine treatment, were usually asymptomatic and therefore were of little clinical relevance.[19] The increased levels of alanine aminotransferase were not associated with any liver damage.[19]

As quetiapine is extensively metabolised by the liver, dosage adjustment may be necessary in patients with schizophrenia with known hepatic impairment, especially during the initial dose-titration period.[19]

3.6 Endocrine System

Quetiapine has very low affinity for dopamine receptors in the tuberoinfundibular dopamine system,[34] and this is considered to account for its minimal effects on plasma prolactin levels.[2] There appears to be no dose-response relationship between quetiapine and plasma prolactin concentration (fig 2).[3]

In contrast, hyperprolactinaemia is an undesirable effect of many antipsychotic agents (including haloperidol, sertindole and risperidone).[3,35-37] Increased prolactin levels lead to reproductive and

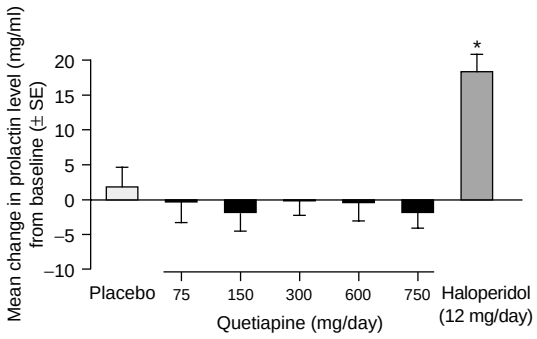

Fig. 2. Comparison of mean change from baseline in prolactin levels after 6 weeks of treatment with quetiapine and haloperidol.[3] **SE** = standard error; * p = 0.008 *vs* placebo.

hormonal adverse effects (e.g. sexual dysfunction, menstrual irregularities, gynaecomastia, galactorrhoea and, in the long term, osteoporosis), and have been shown in young patients with schizophrenia to be a contributor to noncompliance.[38,39] Quetiapine appears to be associated with a low incidence of sexual dysfunction.[40] Spontaneous reporting by 2387 patients receiving quetiapine in controlled clinical trials, has revealed reproductive/hormonal adverse effects in less than 0.1% of patients,[41] consistent with the observation that during these trials quetiapine was not associated with elevations in serum prolactin levels. Moreover, in some clinical trials reductions in prolactin levels were noted with quetiapine compared with other antipsychotic drugs, such as chlorpromazine[5] and haloperidol.[7]

3.7 Thyroid Function

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total and free thyroxine (T_4).[19] The reduction in total and free T_4 was maximal within the first 2 to 4 weeks of quetiapine treatment, with no further reduction during long term therapy. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment.

3.8 Haematology

As with other antipsychotics, leucopenia and/or neutropenia have been observed in patients receiving quetiapine.[19] However, during clinical trials with quetiapine, no cases of persistent severe neutropenia or agranulocytosis were reported.[19] During postmarketing surveillance up to 31 December 1999, there have been 25 cases of neutropenia and 42 cases of leucopenia; resolution of leucopenia and/or neutropenia has followed cessation of quetiapine therapy.[19]

3.9 Ocular Effects

Cataracts were detected in beagle dogs who received quetiapine in dosages of up to 100 mg/kg/day (approximately 4 times the maximum recommended dose in humans on a mg/m^2 basis) after 6 months' treatment.[19] Despite no evidence of lenticular changes being found in other species tested, including 2 one-year monkey studies that included a dose 5.5 times the maximum recommended dose in humans, a precautionary warning appears in the US label.

Patients with schizophrenia have a higher risk for ocular pathology than the general population, including lens opacities (21.7% as reported by Smith et al.[42]). Among the possible causes of eye abnormalities of this population are the effects of antipsychotic medication, especially thioridazine and chlorpromazine, which have long been associated with ocular disturbances. Other potential risk factors associated with cataract formation are: increased age, female gender, high blood pressure, cigarette smoking, alcohol use, dietary deficiencies, and low educational and socioeconomic status.[43]

In a recent case-controlled study, investigators performed a standardised eye examination in a group of patients with schizophrenia and a group from the general population.[44] Different distributions of cataract types were detected in the 2 groups. A specific type of cataract, anterior subcapsular, where opacities are often associated with accumulation of pigment and usually develop with no significant visual impairment, was significantly

more prevalent among patients with schizophrenia (26%) than in the general population (0.2%). When considering all cataract types, the prevalence was similar in both groups.

A very small number (0.004%) of lens opacities were reported in 435 000 patients in the US who received quetiapine in the first 27 months.[19] Careful scrutiny of these 17 reports revealed no evidence of direct linkage to quetiapine treatment. No reports of lens opacities have been received from any other country.

3.10 Bodyweight Gain

All antipsychotic drugs (both typical and atypical) are associated with some degree of bodyweight gain, which, among other mechanisms, may be related to the 5-HT antagonist activity of these drugs. Among the atypical antipsychotics, clozapine and olanzapine appear to be associated with moderate to severe bodyweight gain, whereas quetiapine and risperidone are associated with moderate bodyweight gain.[45] According to manufacturers and information from clinical trials, olanzapine, risperidone and quetiapine were all associated with significantly greater bodyweight gain (≥7% of baseline bodyweight) than placebo (29 *vs* 3%; 18 *vs* 9% and 23 *vs* 6%, respectively).[19]

Analysis of clinical trial and open-label extension phase data (n = 2216) has revealed that treatment with quetiapine resulted in a mean bodyweight increase of 2.08kg (n = 778) over the first 5 to 6 weeks. Similar mean bodyweight increases of 2.16kg (n = 171), 1.85kg (n = 556) and 2.77kg (n = 360) from baseline were observed at 9 to 10 weeks, 6 to 9 months and 9 to 12 months, respectively.[46] The average mean daily dosage of quetiapine for the patients at 9 to 12 months was 428 mg/day. Only 1 patient from the 2216 cohort (0.05%) withdrew because of bodyweight gain. Postmarketing surveillance data as of 31 December 1999 (109 000 to 164 000 patient-years quetiapine exposure) indicate that there have been 42 reports of bodyweight gain.[19]

Preliminary results in patients with schizophrenia who have had bodyweight gain during clozapine therapy show that the addition of quetiapine reverses the clozapine-induced bodyweight gain and improves glycaemic control.[47]

4. Overdose

Experience of overdose with quetiapine is limited. However, during clinical trials there were instances where up to 20g of quetiapine was ingested with no resulting fatalities.[19] Overall, the accompanying signs and symptoms were an exaggeration of the drug's known pharmacological effects, i.e. drowsiness and sedation, hypotension and tachycardia. Patients who had taken an overdose of quetiapine received appropriate therapeutic intervention (including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system), were closely monitored and recovered rapidly.[19]

A recently reported case study[48] describes the sequelae of an intentional overdose of 100 tablets of quetiapine 200mg (total dose 20g) by a 26-year-old female patient who had been taking quetiapine for 1 month concomitantly with other medications, including lorazepam, trazodone and propranolol. Following lavage using activated charcoal the patient was managed in an intensive care setting and within 42 hours had made a complete recovery. Notable events during the recovery period were loss of consciousness and requirement for airway protection (2.5 hours postingestion), recovered consciousness (16 hours postingestion) and sinus tachycardia which lasted for approximately 40 hours postingestion. These sequelae may be explained by the pharmacology of quetiapine.

5. Drug Interactions

In common with other antipsychotics, quetiapine is extensively metabolised in the liver by the cytochrome P450 (CYP) system; the principal isoenzyme responsible for this process is CYP3A4.[19] However, the pharmacokinetics of quetiapine are not significantly altered in patients with hepatic or renal impairment.[49]

Since quetiapine does not appear to inhibit any of the CYP isoenzymes, or induce the CYP3A4 isoenzyme, it is unlikely to interfere with the metabolism of drugs by CYP isoenzymes. However, drugs that affect the activity of the CYP3A4 isoenzymes have the potential to interact with quetiapine. Hence, if quetiapine is used concomitantly with hepatic inducers (e.g. phenytoin, carbamazepine, barbiturates, rifampicin), increased doses of quetiapine may be required to maintain a therapeutic effect.[50] However, the pharmacokinetics of quetiapine were not altered significantly following co-administration of imipramine (a CYP2D6 inhibitor) and only slightly affected following co-administration with fluoxetine (both a CYP3A4 and CYP2D6 inhibitor).[19]

In a multiple-dose trial in 12 healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean peak plasma concentration (C_{max}) and area under the plasma-concentration time curve for quetiapine of 235 and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%.[19] The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean time to C_{max} was unchanged. Because of the potential for an interaction of a similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals and macrolide antibacterials). Special consideration should be given to elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

The pharmacokinetics of quetiapine were not affected by concomitant administration of risperidone or haloperidol.[19] Furthermore, the pharmacokinetics of lithium were not altered when co-administered with quetiapine.[51] However, co-administration with thioridazine increases the clearance of quetiapine and so, if used concomitantly, higher doses of quetiapine may be required.[52] Pimozide may also possibly interact metabolically with quetiapine. [19] Limited data suggest that the effects of cardiac agents are not potentiated by quetiapine, although formal interaction studies with commonly used cardiovascular agents have not been performed.[19]

Given that the effects of quetiapine are primarily on the central nervous system, it should be used with caution in combination with other centrally acting drugs and alcohol. Theoretically, because of its sedative properties, quetiapine may be expected to enhance the effects of other sedative agents (such as alcohol and benzodiazepines), although to date there is no evidence of this.[19]

6. Use in Special Populations

6.1 Elderly

The benign profile of quetiapine makes it suitable for the elderly, who are particularly sensitive to the extrapyramidal effects of antipsychotics.[53] Clinical experience of quetiapine in elderly patients is increasing and data obtained from clinical trials show quetiapine to be well tolerated in this population.

During phase II/III clinical trials, 200 patients aged ≥65 years received quetiapine (median dosage 150 mg/day).[19] The drug was shown to be generally well tolerated, and comparison of its adverse event profile in these trials with that in younger patients revealed similarities in the type, severity and persistence of adverse events. The lack of anticholinergic activity with quetiapine is one of its main advantages in this population.

Data from an open-label 52-week trial of quetiapine (median dosage 100 mg/day) in psychotic patients aged ≥65 years (n = 151) show the drug to be effective and well tolerated.[54] There were decreases in Brief Psychiatric Rating Scale (BPRS) score (total, and positive and negative symptom clusters) and Clinical Global Impression Severity of Illness (CGI-SI) score after 52 weeks (BPRS change = –7.2, $p<0.00001$; CGI-SI change = –0.7, $p<0.0001$). Most of the adverse events reported were mild or moderate. The most common adverse events were somnolence (31%), dizziness (17%) and postural hypotension (15%), consistent with

the increased sensitivity of elderly patients to antipsychotic agents in general.[20] However, no patient was withdrawn from quetiapine treatment and EPS-related adverse events occurred infrequently (6% of patients). Preliminary presentation of the 52-week data from this trial indicates that clinical improvement was maintained and there were no clinically important mean changes in haematological or liver function test results, electrocardiograms or vital signs.[54]

Thus, preliminary data indicate that quetiapine is well tolerated in the elderly, and the risk of adverse effects may be minimised by commencing treatment with a 25mg dose, given once or twice daily, and escalated in 25 to 50mg increments every 1 to 3 days to reach a maintenance dosage, which is likely to be lower than that used in younger patients. As with other antipsychotic drugs, clearance rates of quetiapine are reduced (30 to 50%) in the elderly.[19]

6.2 Adolescents

Experience of the use of quetiapine in the adolescent population is currently limited. A small, open-label study (n = 10) evaluating the pharmacokinetics of quetiapine in adolescents aged 12 to 17 years suggests the safety profile of quetiapine in this population may be similar to that in adult patients.[55] During this study no patient withdrew because of an adverse event.

7. Patient Acceptance, Satisfaction and Long Term Therapy

Quetiapine has demonstrated a good safety profile during long term, open-label extension treatment, very similar to that observed in the short term clinical studies. Preliminary data from 1085 patients with schizophrenia enrolled in open-label extensions to short term clinical trials indicate that quetiapine is well tolerated for up to 2 years.[56] In common with the safety results of the acute trials, the most frequently reported adverse effects were headache, insomnia and somnolence, and the majority of these adverse events were mild or moderate in intensity. Additionally, there were no clinically important mean changes or trends in any other haematology or clinical laboratory values.

Two surveys investigating patients' acceptance of and satisfaction with long term quetiapine therapy have indicated that the drug is well tolerated and is a highly acceptable treatment compared with previously received antipsychotic medications. Kalali[15] studied the perceptions of 30 patients with schizophrenia selected from a group that had been receiving quetiapine in an open-label extension for an average of 4 months, and had been receiving antipsychotic medication for an average of 7.8 years. 85% of patients indicated they preferred quetiapine to earlier treatments and 87% were satisfied with the drug. 47% of patients reported having no adverse effects whilst on quetiapine. Hellewell et al.[16] evaluated the views of 129 patients who had been receiving quetiapine in an open-label trial for at least 6 months (range 6.1 to 47.2 months, mean 19.9 months). Over 75% of patients were very or extremely satisfied with quetiapine (fig. 3). 74% of patients reported no adverse effects, 23.3% mild adverse effects and 2.3% moderate adverse effects over the previous month of treatment (fig. 3). Of those 118 patients who had been previously treated with other antipsychotics, 97% reported that they preferred quetiapine to previous antipsychotic medications, mainly because of better tolerability and greater efficacy (fig. 3). Patients also identified improvements in their quality of life and activities of daily living (fig. 3). In this cohort of patients, it would appear that both antipsychotic efficacy and tolerability are important for patients receiving antipsychotic medication, and that quetiapine's unique balance of these is a positive benefit to patients' overall quality of life that results in improved compliance and treatment outcome.

8. Conclusion

The safety of quetiapine from clinical trials and open-label extension phases has been assessed across the full dosage range of 150 to 750 mg/day. Even at high dosages, treatment with quetiapine has resulted in little EPS and virtually no tardive dyskinesia, and no sustained elevation in plasma

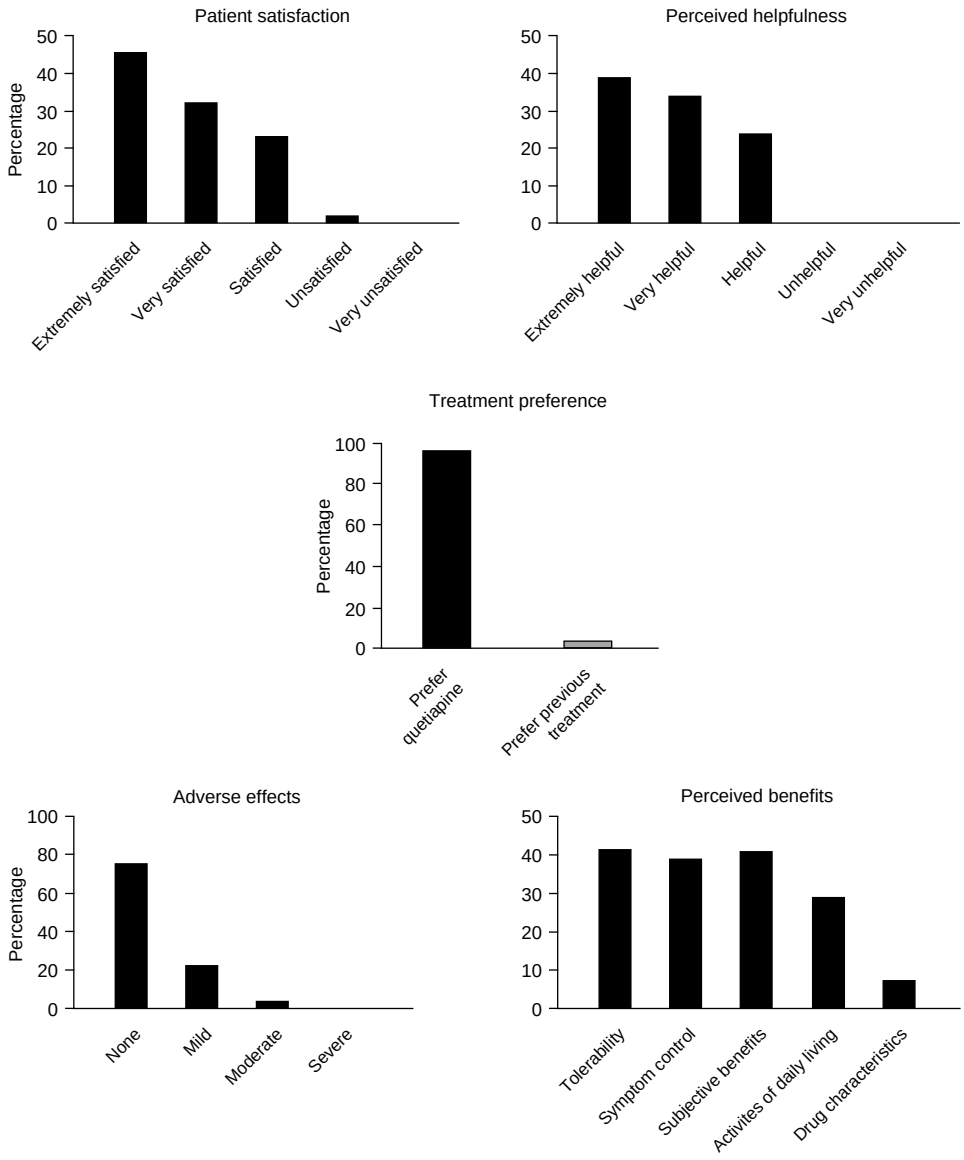

Fig. 3. Patient experience of long term quetiapine therapy. Data obtained from 129 patients with schizophrenia who received quetiapine in an open-label trial for at least 6 months (mean 19.9, range 6.1 to 47.2 months).[16]

prolactin levels. There has been little evidence of the development of seizures or NMS, cardiovascular adverse effects have been mild, and only 1 case of sudden death has been reported. Effects on the gastrointestinal system and liver function have been minimal, while there have been no cases of persistent severe neutropenia or agranulocytosis, and only modest increases in bodyweight. The benign adverse effect profile of quetiapine predicts that it will be advantageous for patients with schiz-

ophrenia, including those who are especially sensitive to adverse effects from medications, such as the elderly and patients in poor general health. Based on a thorough and in-depth review of all clinical and open-label extension data, quetiapine, at the recommended dosage range of 150 to 750 mg/day, has a favourable balance of known benefits against potential risks. Quetiapine is a first-line antipsychotic and it provides a valuable addition to the range of drugs available to the clinician in the management of the serious mental disorder of schizophrenia.

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