Review of Quetiapine Side Effects

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The newest atypical antipsychotic medication to be approved by the U.S. Food and Drug Administration, quetiapine is a drug that awaits a wide range of clinical and head-to-head comparisons. Nevertheless, clinical trials currently available suggest that quetiapine has a beneficial side effect profile, particularly with regard to extrapyramidal symptoms. To date, quetiapine has also proved effective in the treatment of schizophrenia, but its efficacy, while clearly superior to that of placebo, seems no greater than that of haloperidol or chlorpromazine. Clinical trials have supported the use of quetiapine in treating elderly patients. Further research is necessary to establish the clinical profile of quetiapine.
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Quetiapine is the newest atypical antipsychotic to be approved by the U.S. Food and Drug Administration. As a result, there is less information available to date about quetiapine than there is about the other atypical antipsychotics. Nonetheless, the limited number of clinical trials to date confirms preclinical assessments of quetiapine as an atypical antipsychotic[1] and suggests that quetiapine, although not clearly superior to haloperidol[2] or chlorpromazine[3] in efficacy, has a benign side effect profile—particularly with regard to extrapyramidal symptoms (EPS). This side effect profile makes the drug particularly attractive in treating the elderly.

EFFICACY OF QUETIAPINE

In clinical trials, the efficacy of quetiapine was superior to that of placebo and similar to that of conventional antipsychotics.[2,3] Arvanitis et al.[2] evaluated 5 fixed doses of quetiapine (75–750 mg/day) in 361 patients diagnosed with an acute exacerbation of schizophrenia to compare efficacy of quetiapine versus placebo and haloperidol as measured by the Brief Psychiatric Rating Scale. At week 6, the differences from baseline were statistically significant ($p \leq .05$) versus placebo for the 4 highest doses of quetiapine (150, 300, 600, and 750 mg/day), while there were no significant statistical differences between any dose of quetiapine and haloperidol. Peuskens and Link[3] found no statistical differences between quetiapine (mean daily dose = 407 mg) and chlorpromazine (mean daily dose = 384 mg) in a 6-week double-blind study in 201 hospitalized patients. The efficacy of the 2 treatments was similar for both positive and negative symptoms.

A meta-analysis[4] of the randomized controlled trials of quetiapine, olanzapine, risperidone, and sertindole (not marketed in the United States) also revealed that while risperidone and olanzapine are slightly more effective than haloperidol in the treatment of global symptomatology and negative symptoms of schizophrenia, quetiapine is equal to haloperidol for the treatment of overall symptomatology and slightly less effective than haloperidol in the treatment of negative symptoms.

QUETIAPINE EFFECTS AT THE RECEPTOR SITES

An examination of the receptor site activity induced by quetiapine will shed light on the side effect profile of the drug. One or more receptors can have actions that cause similar side effects, but the side effects of quetiapine remain mild nonetheless.

Histaminic

Quetiapine blockade of the histaminic (H_1) receptor (IC_{50} = 30 nM) is very high. This blockade causes sedation in 18% and dizziness in 10% of patients.[5] The sedation is an effect not only of the H_1 blockade but also of α_1-adrenergic blockade. Quetiapine produces substantially fewer EPS than placebo. In a fixed-dose trial of quetiapine,[2] patients' improvements on the Simpson-Angus Neurologic Rating Scale increased as the dosage of quetiapine increased (Figure 1). Goldstein and Arvanitis[6] have indicated that blockade of H_1 receptors inhibits response

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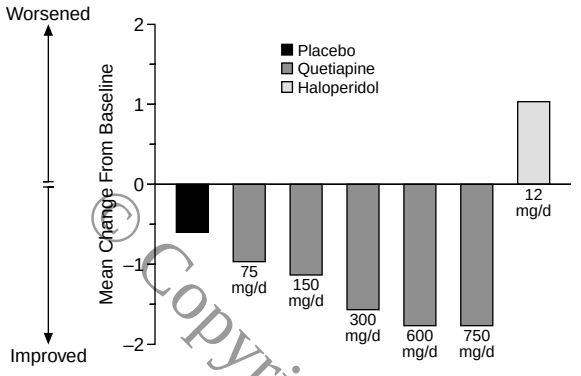
Figure 1. A Fixed-Dose Trial of Quetiapine, Haloperidol, and Placebo: Simpson-Angus Neurologic Rating Scale Total Scores[a]



[a]Data from reference 2.

to acetylcholine through muscarinic receptors, and so, as with diphenhydramine, quetiapine functionally decreases the amount of activation or acetylcholine predominance associated with EPS—potentially a major advantage for quetiapine over currently available antipsychotics.

Histaminic blockade is also linked to weight gain, which can be a serious adverse effect of quetiapine. In the 3- to 6-week placebo-controlled clinical trials, 23% of quetiapine-treated patients met a weight gain criterion of 7% or more of body weight compared with 6% of the patients taking a placebo.[5]

α_1-Adrenergic

Like histaminic blockade, quetiapine blockade of the α_1-adrenergic (A_1) receptor (IC_{50} = 94 nM) also causes somnolence at a rate of 7% and dizziness at a rate of 6%. In addition, this blockade causes some orthostatic hypotension. In adults, orthostatic hypotension is reported as dizziness in 6% of patients; in the elderly, the rate can be 20% or greater. Dizziness is not always caused by orthostatic hypotension. It is found in many patients taking atypical antipsychotics in the absence of orthostatic hypotension. More than 20% of elderly patients receiving quetiapine—usually in doses of 100 to 200 mg/day—show an increase in heart rate of 20 beats per minute or greater or a decrease in systolic blood pressure of 30 mm Hg or greater. Orthostatic hypotension needs to be watched very carefully in older persons because falls attributable to orthostatic hypotension, combined with age-related bone loss, can lead to bone fractures.[7]

Serotonergic

Quetiapine blockade of the serotonergic (5-HT_{2A}) receptor (IC_{50} = 148 nM), along with the histaminic activity, contributes to the EPS-inhibiting effects of the drug.[6] The rate of EPS in patients taking quetiapine is very low. McManus et al.,[8] reporting after 12 weeks of an ongoing open-label study of quetiapine in 151 elderly patients with DSM-IV diagnoses of psychotic disorders, found that adverse events due to EPS occurred in 6% of the study population. Doses ranged from 25 to 800 mg/day. In the Arvanitis et al.[2] clinical trial, the incidence of EPS was no more common in patients taking any dose of quetiapine than it was in patients taking a placebo. While no patients treated with quetiapine withdrew from the study because of EPS, 4 patients taking haloperidol and 1 patient taking a placebo withdrew due to EPS. The Barnes Rating Scale for Drug-Induced Akathisia revealed substantial superiority for quetiapine at day 42 in the Peuskens and Link trial.[3] Quetiapine users had a low incidence of treatment-emergent EPS. Small et al.[9] investigated the effects of low doses (≤ 250 mg/day) and high doses (≤ 750 mg/day) of quetiapine and placebo in 286 patients with a DSM-III-R diagnosis of chronic or subchronic schizophrenia. The researchers found that quetiapine did not induce EPS. Borison et al.[10] conducted a 6-week, double-blind, placebo-controlled trial of 75 to 750 mg/day of quetiapine in 109 patients with a DSM-III-R diagnosis of acute chronic or subchronic schizophrenia. They found that patients treated with quetiapine in the dose range studied failed to experience EPS. The serotonergic activity of quetiapine may also be responsible, in large part, for the drug's antipsychotic properties, although this connection remains controversial.[6]

Dopaminergic

Quetiapine blockade of the dopaminergic (D_2) receptor (IC_{50} = 329 nM)—combined with the histaminic and serotonergic effects of the drug—results in no reported cases of dystonias, parkinsonian symptoms, or akathisia.[4,6] This low affinity for the D_2 receptor—2% when methylspiperone[11] is used as a ligand in positron emission tomography (PET) studies and 20% to 50% when raclopride is used[12]—is considerably less with therapeutic doses of quetiapine than with the traditional antipsychotic drugs, a property shared with clozapine.

The low affinity of quetiapine for the D_2 receptor may have some very important implications that have not yet been suggested by the clinical data. Quetiapine has less affinity for the D_2 receptor than does dopamine itself. With pulsatile release of dopamine into the synapse, Seeman et al.[13] have suggested that the blockade of D_2 receptors by quetiapine is intermittent, at best, when it occurs and that quetiapine is displaced from the receptor with each volley of dopamine released into the synapse. If so, that fact is important in terms of EPS. Ultimately, this intermittent blockade may also be very important with respect to tardive dyskinesia. Currently, we lack data on quetiapine in tardive dyskinesia.

Quetiapine, with its very low or very temporary D_2 occupancy, produces no prolactin elevation. Arvanitis et al.[2]

found, in their fixed-dose study, that no dose of quetiapine produced greater levels of prolactin elevation than placebo or haloperidol. In fact, patients taking quetiapine showed small decreases in prolactin levels from baseline measurement, changes that were not significant when compared with those of patients taking a placebo but that were significant ($p = .0075$) when compared with those of patients taking haloperidol. Similarly, Peuskens and Link,[3] Small et al.,[9] and Borison et al.[10] failed to find sustained elevations of prolactin levels associated with quetiapine use.

Because the D_2 blockade of quetiapine does not produce prolactin elevation, it is assumed that such a blockade would produce less galactorrhea than in patients taking typical antipsychotics. It also seems reasonable to assume that patients taking quetiapine will show less drug-induced sexual dysfunction than patients taking typical antipsychotics.

Muscarinic

Quetiapine blockade of the muscarinic (M_1) receptor (IC_{50} = 5000 nM) does not result in dry mouth, constipation, or urinary retention.[6] However, this blockade does produce an interference with the effects of acetylcholine by the H_1 block.

OCULAR SIDE EFFECTS

Although chronic canine studies reported cataract development associated with quetiapine use, cataracts failed to emerge in 2 studies of monkeys lasting 1 year. In addition, lens changes—minor in nature and likely age-related—were comparable to a control group taking haloperidol in a long-term clinical trial. Across all controlled clinical trials, the proportions of patients with lens changes were similar in groups taking quetiapine, haloperidol, and placebo. Although no relationship has been established between quetiapine use and cataract development in humans, ocular examinations are recommended.[5]

CONCLUSION

The efficacy of quetiapine is superior to that of placebo and comparable to that of conventional antipsychotics. Low rates of EPS and no reports of sustained increases in serum prolactin levels with quetiapine have been confirmed by clinical trials conducted to date, which have also reported substantial weight gain in up to 23% of patients. More clinical trials are needed to explore the properties of this new atypical antipsychotic medication.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, clozapine is not approved by the U.S. Food and Drug Administration for the treatment of schizoaffective disorder.

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