Use of Quetiapine in Elderly Patients

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Behavioral problems associated with psychosis in the elderly have a significant negative impact on patients' quality of life and can lead to placement in a nursing home. Because of their decreased propensity to produce extrapyramidal symptoms, atypical antipsychotics such as quetiapine hold promise in the treatment of these vulnerable patients. Quetiapine may, in theory, be particularly advantageous in this regard because of its lack of anticholinergic activity and its relatively loose binding to dopamine receptors. This article reviews the somewhat limited number of clinical studies of the use of quetiapine in treating older patients with schizophrenia and other psychotic disorders, patients with psychosis associated with Alzheimer's disease or dementia with Lewy bodies, and patients with Parkinson's disease and drug-induced psychosis. *(J Clin Psychiatry 2002;63[suppl 13]:21–26)*

Psychotic symptoms are surprisingly common in older adults, with a lifetime incidence of nearly 25%[1] and prevalences ranging from 0.2% to 4.7% in community-based samples to 10% to 63% in nursing home populations.[2] The main categories of late-life psychoses include dementia with psychotic symptoms, late-onset schizophrenia, delusional disorder, early-onset psychotic disorders persisting to late life, late-onset mood disorders, psychotic disorders caused by medical conditions or medications, and delirium.[3] Agitation and aggressiveness are associated with psychosis in the elderly and frequently are the precipitating reasons for psychiatric consultation.[1]

At the same time, treatment of psychiatric disorders in the elderly is complicated by a high frequency of comorbid medical illnesses and concomitant medications, risk of side effects, and age-related changes in pharmacodynamics and pharmacokinetics.[4] Typical adverse effects of antipsychotics in this population include sedation, orthostatic hypotension, and extrapyramidal symptoms (EPS).[5] There is also evidence that antipsychotics, by virtue of their inhibitory effects on dopaminergic, cholinergic, and histaminergic neurotransmission, may produce deleterious cognitive effects in some elderly patients.[6] Compared with the use of typical antipsychotics, the use of atypical antipsychotics is generally associated with a reduction in the frequency of acute EPS and a reduced need for concomitant antiparkinsonian drugs.[7]

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The various atypical antipsychotics possess different neurotransmitter receptor binding properties that may translate into treatment advantages for different patient populations. Antipsychotics that block dopamine receptors in the striatum in a manner that allows dopamine to maintain its physiologic neurotransmitter role, such as quetiapine, could theoretically be advantageous when used for conditions associated with diminished dopamine function, for example, Parkinson's disease.[6] Similarly, drugs with weak anticholinergic effects, such as quetiapine and risperidone, could be advantageous for treating patients with impaired cholinergic function, for example, Alzheimer's disease. This article reviews the clinical evidence (Table 1) regarding the use of quetiapine in treating various populations of elderly patients. Some of the evidence results from open-label, as well as placebo-controlled clinical trials addressing specific hypotheses, while other results from case series, chart reviews, or subanalyses of larger studies. While some reports have been published in peer-reviewed journals, many have not. For these reasons, while trends emerge across these studies, caution is warranted in interpreting this review.

PARKINSON'S DISEASE AND DRUG-INDUCED PSYCHOSIS

Psychotic symptoms occur in up to 40% of patients with Parkinson's disease and other degenerative parkinsonian disorders.[8] Psychotic symptoms affect the quality of life for patients with Parkinson's disease and their families and may lead to placement in a nursing home.[8] These psychotic symptoms occur because of both the underlying neuropathology of Parkinson's disease and the adverse effects associated with chronic antiparkinsonian drug administration.[9] Although the addition of antipsychotic drugs or the withdrawal of antiparkinsonian drugs

Table 1. Summary of Reports of Quetiapine in the Treatment of Elderly Patients[a]

Clinical Trial	N	Duration	Type of Study	Overall Efficacy	Safety and Tolerability
Parkinson's Disease					
Evatt et al, 1996[20]	10	3 mo	Open-label	Improvement in BPRS scores	Improvement in UPDRS motor scores
Juncos et al, 1998[16]	15	52 wk	Open-label	Improvement in BPRS scores	Improvement in UPDRS motor scores
Parsa and Bastani, 1998[19]	2	52 wk	Open-label	Psychotic symptoms controlled	No worsening of motor function
Friedman et al, 1999[21]	44	1 mo	Open-label	Improvement in BPRS scores	Improvement in cognition
Juncos et al, 1999[17]	40	52 wk	Open-label (subgroup from larger study)	BPRS and CGI-S improved significantly	Improvement in motor function
Fernandez et al, 1999[13]	35	4 wk	Open-label	Improvement in psychosis (20/24)	No decline in motor function; 3/24 withdrew due to side effects
Menza et al, 1999[18]	3	3–6 mo	Open-label	Behavioral improvement	No increase in parkinsonism
Fernandez et al, 2000[23]	15	2 mo	Open-label	Improvement in BPRS scores	Improvement in UPDRS motor scores
Targum and Abbott, 2000[14]	11	52 wk	Open-label (subgroup from larger study)	Controlled visual hallucinations (6/10); less effective for paranoia or delusions	6 patients withdrew; no exacerbation of parkinsonism
Juncos et al, 2001[22]	29	24 wk	Open-label	Improvement in BPRS total and CGI-S scores Improvement in cognition (memory, sustained attention)	Improvement in UPDRS motor scores
Roberts et al, 2001[12]	25	24 wk	Open-label, placebo-controlled	Improvement in psychotic symptoms and cognition	No deterioration in motor symptoms
Fernandez et al, 2002[24]	87 (PD) 11 (DLB)	NA	Open-label, retrospective chart review	Partial to complete resolution of psychosis in 80% (70/87) of patients with PD and 90% (10/11) of patients with DLB	Motor worsening noted in 32% (28/87) of patients with PD and 27% (3/11) of patients with DLB
Juncos et al, 2002[15]	27	36 mo	Retrospective chart review, quetiapine vs clozapine	Both clozapine and quetiapine significantly reduced hallucinations and agitation	63% still on quetiapine 50% still on clozapine
Dementia					
Schneider et al, 1999[41]	78	52 wk	Open-label (subgroup from larger study)	Improvement in BPRS total score and BPRS hostility subscale score	Improvement in motor function (SAS score); no change in mean AIMS score
Juncos et al, 2000[45]	10	21 ± 10 mo	Open-label	Significant improvement in BPRS anxiety, hallucinations, and agitation subscale scores	Most patients did not experience serious adverse events or significant EPS
Parsa et al, 2001[44]	10	52 wk	Open-label	All patients showed improvement in BPRS scores	No significant worsening in motor function or cognitive status
Parsa et al, 2001[47]	30	NA	Retrospective chart review of quetiapine plus donepezil	All patients showed improvements in symptoms	No worsening of motor function
Elliot and Elliott, 2001[42]	3	12 wk	Open-label	Improvement in psychotic symptoms (3/3) and cognitive function (2/3)	No increase in EPS
Tariot et al, 2002[40]	284	10 wk	Double-blind, placebo-controlled; quetiapine and haloperidol	All treatment groups showed improvement on BPRS total scores	Quetiapine patients had fewer EPS than haloperidol and placebo patients
Baskys and Davis, 2002[43]	5	6 wk	Open-label	Significant improvement in some psychotic symptoms	No increase in EPS
Schizophrenia[b]					
Vinogradov et al, 2000[31]	32	52 wk	Open-label (subgroup from larger study)	Significant improvement in BPRS and CGI-S	EPS improved
Tariot et al, 2000[30]	184	52 wk	Open-label	Significant improvement in BPRS and CGI-S	52% withdrew; EPS (13%), somnolence (31%), dizziness (17%), postural hypotension (15%)
Mintzer et al, 2001[29]	92	4 mo	Open-label; quetiapine vs risperidone	Both quetiapine and risperidone improved psychotic symptoms	EPS significantly less in quetiapine vs risperidone
Madhusoodanan et al, 2000[32]	7	12–42 d	Open-label	4/7 responded with decrease in positive and negative symptoms	EPS decreased in 3 patients; transient hypotension and somnolence (2/7)

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, DLB = dementia with Lewy bodies, EPS = extrapyramidal symptoms, NA = not available, PD = Parkinson's disease, SAS = Simpson-Angus Scale, UPDRS = Unified Parkinson's Disease Rating Scale.
[b]Includes studies with multiple categories of patients in addition to patients with schizophrenia.

may improve the behavioral problems, these strategies usually worsen the motor difficulties. The tendency of typical antipsychotics to produce EPS is exacerbated in these patients. Consequently, the treatment of Parkinson's disease may provide the most stringent test of an antipsychotic's freedom from inducing parkinsonian motor symptoms,[10] with atypical antipsychotics better in this respect than typical antipsychotics.[5,11]

Efficacy

In a 24-week trial conducted by Roberts et al.,[12] 25 patients with Parkinson's disease received a maximum of 400 mg/day of quetiapine. Treatment was effective in lessening psychotic symptoms, as demonstrated by significant improvement in both Brief Psychiatric Rating Scale (BPRS) total and Clinical Global Impressions-Severity of Illness (CGI-S) scale scores, which was maintained throughout the entire 24 weeks. Quetiapine treatment also appeared to have beneficial effects on cognition, with significant improvement seen in Unified Parkinson's Disease Rating Scale (UPDRS) mental subscale scores and in memory tests. Specifically, patients treated with quetiapine exhibited significant improvement in recall and nominal improvement in sustained attention, whereas a control group of 25 nonpsychotic patients with Parkinson's disease not treated with quetiapine exhibited no change in recall and a significant decline in sustained attention over 6 months. These results suggested that quetiapine might improve both cognitive function and psychotic symptoms in these patients.

In a short-term (4-week), open-label pilot study of 35 patients with Parkinson's disease who were treated for psychosis, treatment with quetiapine at a mean dose of 40 mg/day produced a clinically and statistically significant improvement in the mean BPRS total scores.[13] Improvement of psychosis was noted in 20 of 24 neuroleptic-naive patients.

Several long-term, open-label studies in patients with Parkinson's disease have been reported.[12,14–17] In the study by Targum and Abbott,[14] 11 patients with Parkinson's disease and acute psychosis received doses of quetiapine between 25 and 300 mg/day. Nine of the patients completed at least 12 weeks of treatment, and 5 completed the 52 weeks of the study. Quetiapine improved psychotic features in 7 of 10 patients.

In a subanalysis of 40 patients with advanced Parkinson's disease who were part of a larger 1-year trial of quetiapine in elderly patients with psychosis (N = 169),[17] quetiapine at a mean dose of 75 mg/day was effective in improving psychotic symptoms, as demonstrated by significant improvement in BPRS total and CGI-S scores. The improvement was clinically evident in virtually all of these patients and was maintained throughout the entire 52 weeks of the trial.

In other studies and case reports,[18–21] treatment with quetiapine produced significant improvement in psychotic symptoms in patients with Parkinson's disease. In a 24-week study,[22] quetiapine was effective in 29 patients who had failed previous treatment with other atypical antipsychotics.[22] In another study,[23] 12 of 15 patients with Parkinson's disease were successfully switched from clozapine to quetiapine without observable loss of antipsychotic effect or significant worsening of parkinsonian symptoms.[23]

A retrospective chart review of 27 patients with Parkinson's disease and hallucinations who were treated with quetiapine (N = 23) or clozapine (N = 4) for an average of 36 months[15] found that both quetiapine and clozapine caused a sustained reduction in hallucinations (100% to 59%, $p < .01$) and a trend toward reduced agitation (37% to 19%, $p < .06$). In another retrospective chart review of 87 patients with Parkinson's disease and drug-induced psychosis,[24] quetiapine treatment (mean dose = 58 mg/day) for a mean duration of 14 months produced partial to complete resolution of psychosis in 80% of the patients.[24] These results support the view that both quetiapine and clozapine may have long-term benefits in patients with Parkinson's disease and drug-induced psychosis.

Safety and Tolerability

In the 24-week study by Roberts et al.,[12] there was no deterioration in motor symptoms of Parkinson's disease, along with no clinically important effects on mean vital signs, weight, clinical laboratory tests, and electrocardiograms. In the 4-week, open-label study by Fernandez et al.,[13] no decline in motor function occurred. Three of 24 antipsychotic-naive patients were unable to tolerate quetiapine because of orthostatic hypotension, headache, nausea, and persistence of hallucinations. In the 52-week, open-label study by Targum and Abbott,[14] quetiapine was well tolerated in all but 1 patient who became dizzy during the first week and withdrew from the study. Quetiapine did not exacerbate parkinsonian symptoms, but there was a gradual worsening of motor dysfunction consistent with the progression of Parkinson's disease, as measured by the UPDRS. In the subanalysis of 40 patients with Parkinson's disease,[17] treatment with quetiapine did not worsen the motor symptoms of Parkinson's disease. On the contrary, a significant initial improvement was noted through week 12. In the long-term retrospective chart review study by Juncos et al.,[15] the percentage of patients who were still taking their initial antipsychotic was 63% for quetiapine and 50% for clozapine. These continuation rates suggest that the antipsychotics were well tolerated by the patients. In the retrospective chart review by Fernandez et al.,[24] motor worsening was noted in 32% of the patients with Parkinson's disease and 10 patients discontinued quetiapine because of increased parkinsonism. However, some of the increase in parkinsonism may have been due to disease progression.

SCHIZOPHRENIA

Elderly patients with schizophrenia can experience either new-onset disease or the progression of earlier-onset

disease. Patients with early-onset or late-onset schizophrenia have similar characteristics such as family history of schizophrenia, presence of minor physical anomalies, early childhood maladjustment, severity of positive symptoms, overall pattern of neuropsychological deficits, and qualitative response to antipsychotic medications.[25] The clinical presentation of elderly patients with late-onset schizophrenia shows a lower prevalence of premorbid dysfunction, negative symptoms, and formal thought disorder.[26] For patients with early-onset schizophrenia, the prevalent symptoms change as the patients mature, with both delusions and hallucinations becoming less common and less frightening.[27] At the same time, patients with late-onset schizophrenia tend to respond to lower doses of antipsychotic medications,[25] and there is the suggestion that they may respond better to all antipsychotics.[27]

Efficacy

A subanalysis of elderly patients (≥ 65 years of age) enrolled in an open-label study (Quetiapine Experience with Safety and Tolerability [QUEST])[28] examined the relative efficacy, safety, and tolerability of quetiapine and risperidone.[29] Of the 92 patients, 65 received quetiapine (median dose = 200 mg/day) and 27 received risperidone (median dose = 3 mg/day). Treatment with both quetiapine and risperidone significantly improved psychotic symptoms versus baseline ($p < .01$), as assessed using the Positive and Negative Syndrome Scale.[29] There was no significant difference between the 2 treatments in the degree of improvement of psychotic symptoms.

The effects of long-term (52-week) administration of quetiapine to elderly patients (≥ 65 years of age) were explored in an open-label trial in 184 patients with psychotic disorders, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.[30] Most of the patients (72%) had psychotic disorders due to medical conditions such as Alzheimer's disease, and 28% had schizophrenia or other psychotic disorders. In a subanalysis of the 32 patients with schizophrenia,[31] a median quetiapine dose of 150 mg/day was achieved for a median duration of 319 days. Clinically significant improvement at endpoint was achieved by 47% of the patients, and, furthermore, progressive improvements in BPRS and CGI-S scores were noted.

In an open-label study of quetiapine treatment of 7 hospitalized patients (aged 61 to 72 years) with psychosis,[32] 2 of 4 patients with schizophrenia, 1 of 2 with schizoaffective disorder, and 1 with bipolar disorder showed marked improvement.[32] All 7 patients had previously failed treatment with conventional antipsychotics or other atypical antipsychotics.

Safety and Tolerability

In the analysis of the elderly subgroup from the QUEST trial,[29] "substantial" EPS (requiring dosage adjustment or EPS medication) occurred significantly less often in patients treated with quetiapine ($p < .03$). Furthermore, quetiapine was significantly less likely than risperidone to cause akathisia or hypertonia. In the 52-week, open-label study by Tariot et al.,[30] the most common adverse events in the overall sample were somnolence (31%), dizziness (17%), and postural hypotension (15%), but these adverse events rarely resulted in withdrawal from therapy. An analysis of these events over time showed that they generally occurred during the first weeks of the study. Finally, EPS-related adverse events occurred in 13% of the patients, including those with Parkinson's disease. In the subanalysis of 32 patients with Alzheimer's disease who were treated for 52 weeks with quetiapine,[31] the most common drug-related adverse events were somnolence (6 patients; 19%), dizziness (4 patients; 13%), and postural hypotension (4 patients; 13%).[31] At the same time, motor function improved as evidenced by decreases in Simpson-Angus Scale and Abnormal Involuntary Movement Scale scores early in the trial, consistent with effects of withdrawal from prior therapy and lack of worsening with new treatment. In all of these studies, quetiapine was effective in reducing psychotic symptoms and was not associated with significant adverse effects.

DEMENTIA

Psychotic and behavioral symptoms are common in patients with dementia and include delusions and hallucinations, aggression and combativeness, sleep disorders, anxiety, and depression.[33] Behavioral disorders, rather than cognitive disorders, are the main precipitant of nursing home admission.[34] Antipsychotics are moderately effective for the treatment of agitation or psychosis in patients with dementia who require medication.[35–37] Management of psychosis and behavioral disturbances associated with dementia, however, is difficult because of the risk of worsening EPS and anticholinergic side effects.

These side effects are of a concern in all patients with dementia, including those with Alzheimer's disease, the most common dementia diagnosis. Dementia with Lewy bodies (DLB) may be the second most common cause of dementia, accounting for between 12% to 20% of cases in the elderly.[38] DLB is a progressive disorder associated with fluctuating levels of cognitive impairment, prominent visual hallucinations, spontaneous motor features characteristic of Parkinson's disease, and repeated unexplained falls.[39] The psychotic symptoms associated with DLB pose an especially difficult management problem because of the risk of adverse effects, particularly severe EPS or orthostatic hypotension, which may result in an increased risk of falls as well as other adverse outcomes.[38]

Efficacy

A subanalysis was reported recently in abstract form of a subset of 284 patients with Alzheimer's disease who

were part of a larger group of elderly patients (N = 378) with dementia and psychosis enrolled from 46 nursing homes.[40] In this double blind, placebo-controlled, 10-week, randomized trial, flexible dosing of quetiapine and haloperidol was used. Ninety-one patients were randomly assigned to quetiapine (median daily dose = 96.9 mg; range, 25.0–275.7 mg), 94 to haloperidol (median daily dose = 1.9 mg; range, 0.5–3.5 mg), and 99 to placebo. All treatment groups improved from baseline on BPRS total scores without any treatment affecting psychotic symptoms. However, patients treated with quetiapine and haloperidol showed significantly more improvement on the BPRS agitation subscale than patients treated with placebo. Patients in the quetiapine group also had significantly better functional status as assessed by the BPRS anergia factor, the Physical Self-Maintenance Scale, and the Multidimensional Observation Scale for Elderly Subjects compared with patients treated with haloperidol.

In a subanalysis of 78 patients with Alzheimer's disease who were part of a larger 1-year, open-label trial of quetiapine in elderly patients with psychosis (N = 189),[41] patients received a median dose of quetiapine of 100 mg/day. Significant improvement over baseline score occurred at all time points for BPRS total, BPRS Factor V (mean of hostility, suspiciousness, uncooperativeness), the BPRS hostility item, and BPRS hostility cluster (mean of anxiety, tension, hostility, suspiciousness, uncooperativeness, excitement) scores. Significant improvement in the BPRS positive symptom cluster score was seen at weeks l2 and 24 for Alzheimer's disease patients. Regression analysis suggested that some of the improvement in hostility scores was independent of the improvement in positive symptoms. These results suggest that quetiapine treatment may produce improvement in symptoms of hostility in patients with psychoses related to Alzheimer's disease.

Quetiapine has also been studied in patients with DLB.[24,42–45] By way of example of these preliminary reports, in an open-label, 21 ± 10-month study in 10 patients with clinically probable DLB,[45] psychotic symptoms ranged from drug-induced hallucinations to fixed delusions and agitation. The median final dose of quetiapine was 50 mg/day (range, 12.5–400 mg/day). Anxiety, hallucinations, and agitation, as assessed by the BPRS, remained significantly improved throughout the study. In another open-label, 52-week trial in 10 patients with DLB,[44] all of the patients showed marked improvement in psychosis as measured by the BPRS with good tolerability. In a retrospective chart review of 11 patients with DLB,[24] quetiapine treatment (mean dose = 69 mg/day) produced partial to complete resolution of psychosis in 90% of the patients.[24]

Safety and Tolerability

In the subanalysis of patients with Alzheimer's disease who were residing in nursing homes,[40] patients treated with quetiapine experienced statistically significantly fewer EPS adverse events than patients treated with haloperidol or placebo. Of the treatment-emergent adverse events, somnolence occurred statistically more often during treatment with quetiapine and haloperidol than with placebo. Patients treated with either quetiapine or haloperidol experienced fewer anticholinergic effects such as dry mouth or constipation than did patients treated with placebo. Fewer patients receiving quetiapine experienced falls or fractures than did patients in the other treatment groups. No increase in EPS was noted in most of the other studies of patients with DLB being treated with quetiapine.[42–44] In the study of patients with DLB by Juncos et al.,[45] 3 patients (30%) developed EPS and discontinued treatment with quetiapine; however, there was no change in the measures of EPS in the remaining 7 patients (70%). No worsening of cognition was noted for patients enrolled in a prospective, open-label, 12-week pilot study of outpatients with Alzheimer's disease.[46] In the retrospective chart review of quetiapine plus donepezil by Parsa et al.,[47] no worsening of motor function was reported for any patients. In the retrospective chart review of 11 patients with DLB,[24] motor worsening was noted in 27% of the patients; however, none of the patients discontinued treatment due to motor worsening.[24] These findings underscore the safety and tolerability of quetiapine in elderly patients with dementia.

SUMMARY

Behavioral problems associated with psychosis in the elderly can occur across multiple diagnoses, can have a significant negative impact on the patient's quality of life, and can result in institutionalization. Atypical antipsychotics are less likely to produce EPS than typical antipsychotics and are therefore promising treatment options for this vulnerable patient population. Quetiapine may be particularly advantageous in these vulnerable diagnostic groups because of its good efficacy and tolerability profile.

Data from rigorously controlled randomized clinical trials are generally lacking in this population. Data from open-label studies suggest that quetiapine may be both effective and well tolerated in elderly patients with schizophrenia, dementia, or drug-induced psychosis associated with Parkinson's disease. Details from these large, placebo-controlled trials in dementia have not been published yet.[40] The available data suggest that quetiapine is unlikely to cause worsening of EPS and has generally good overall tolerability, making it an attractive candidate for the treatment of psychotic symptoms in elderly patients.

Drug names: clozapine (Clozaril and others), donepezil (Aricept), haloperidol (Haldol and others), quetiapine (Seroquel), risperidone (Risperdal).

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