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Quetiapine treatment for behavioural and psychological symptoms of dementia in Alzheimer's disease patients: a 6-week, double-blind, placebo-controlled study

D. Paleacu[1]*, Y. Barak[2], I. Mirecky[2] and D. Mazeh[2]

[1]*Neurology Service and Memory Clinic, Abarbanel Mental Health Center, Bat-Yam, Israel, Affiliated with the Sackler School of Medicine, Tel Aviv University, Israel*
[2]*Psychogeriatric Department, Abarbanel Mental Health Center, Bat-Yam, Israel, Affiliated with the Sackler School of Medicine, Tel Aviv University, Israel*

SUMMARY

Setting Treating elderly patients with Alzheimer's disease (AD) and behavioral and psychological symptoms of dementia (BPSD) is challenging due to the increased risk of iatrogenic movement disorders with old neuroleptics and the seemingly increasing risk of cardiovascular events with newer atypical agents. Quetiapine is an atypical antipsychotic agent that warrants further investigation.
Objectives To assess tolerability, safety, and clinical benefit of quetiapine in AD patients with BPSD.
Participants and design AD patients with BPSD participated in a 6-week randomized, double-blind, placebo-controlled trial. Quetiapine was increased on the basis of clinical response and tolerability. Primary efficacy assessments included the Neuropsychiatric Inventory (NPI) and Clinical Global Impression of Change (CGI-C). Secondary efficacy measures included the Mini-Mental State Examination (MMSE), the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movement Scale (AIMS).
Results Forty patients (26 women), mean age 82.2 (SD 6.4) years were enrolled, 27 completed treatment. Median dose of quetiapine was 200 mg/day. Significant NPI total scores reductions (79% for placebo and 68.5% for quetiapine) were observed. The CGI-C score decreased significantly in the quetiapine group ($p = 0.009$ at 6 weeks) and did not change significantly in the placebo group ($p = 0.48$). The MMSE, AIMS, SAS scores and adverse events did not differ significantly between the two arms.
Conclusions Quetiapine did not significantly improve psychosis scores. It did not cause cognitive and motor deterioration. These results might possibly be due to small sample size. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — quetiapine; Alzheimer's disease; psychosis

INTRODUCTION

Dementia is a multidimensional disease characterized by progressive cognitive decline, behavioral symptoms and decline in activities of daily living (Reisberg *et al*., 1986; American Psychiatric Association, 1994; Jost and Grossberg, 1996). The behavioral and psychological symptoms of dementia (BPSD) (aggression, agitation, purposeless wandering, pacing and psychotic symptoms) have a severe impact on patients' quality of life and create severe stress for caregivers, complicating effective management. These symptoms have been described as the main predictor of caregiver burden and cause of negative feelings toward patients (Coen *et al*., 1997). In addition, such symptoms often underlie the decision to institutionalize patients (Ferris *et al*., 1987).

The majority of patients with dementia ultimately require pharmacological interventions to manage BPSD. Agents used include: antipsychotics, anxio-

*Correspondence to: D. Paleacu, Neurological Service and Memory Clinic, Abarbanel Mental Health Center, 15 Keren Kayemet, 59110 Bat Yam, Israel. E-mail: paleacu@post.tau.ac.il

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lytics, antidepressants, beta-blockers and anticonvulsants (Kunik *et al*., 1998).

Second generation (atypical) antipsychotic (SGA) drugs are widely used to treat psychosis, aggression and agitation in patients with Alzheimer's disease, but their benefits are uncertain and adverse effects offset advantages in their efficacy for the treatment of psychosis, aggression or agitation in patients with Alzheimer's disease. (Schneider *et al*., 2006).

Amongst the second generation antipsychotics (SGA), clozapine (Oberbolzer *et al*., 1992), risperidone (De Deyn *et al*., 1999) and olanzapine (Street *et al*., 2001) in low doses seem to be very effective, but not devoid of side effects. The advantage of these drugs is that they impair cognition less than the conventional antipsychotics, and this has already been established in elderly patients with schizophrenia (Meltzer and McGurck, 1999).

Recently, in response to the meta-analysis published by Schneider *et al*. (2005a), the FDA issued an advisory stating that atypical antipsychotic medications when compared with placebo increase mortality among elderly patients due to increased risk of cerebrovascular events (CVA) (Schneider *et al*., 2005a). Another study by the same author examined the risk for CVA in quetiapine-treated patients and found that there is no evidence of increased or decreased risk of CVAs with quetiapine (Schneider *et al*., 2005b).

Quetiapine fumarate (Seroquel®) is one of the most recently introduced SGA and is indicated for the treatment of acute and chronic psychoses, including schizophrenia. Quetiapine, a compound close to clozapine, but devoid of hematological side effects, seems to be an ideal candidate treatment for elderly patients with psychotic symptoms, such as Parkinson's (PD) and Alzheimer's disease (AD) patients.

Most large studies of quetiapine in elderly patients with psychosis (Tariot *et al*., 2000, 2004) were open-label trials suggesting good tolerability with apparent behavioral benefit and few extrapyramidal symptoms (EPS) in most patients. This feature of the drug seems to be one of its most important advantages over other SGA in the elderly (Baskys, 2004; Mintzer *et al*., 2004). Three recent papers (Ballard *et al*., 2005; Tariot *et al*., 2006; Zhong *et al*., 2007), all randomized double blind placebo controlled trials show no benefit of quetiapine over the planned comparisons (haloperidol, rivastigmine or placebo).

As a result of the FDA warning issued against atypical neuroleptics Wang *et al*. (2005) conducted a retrospective study to compare risk of death among elderly patients treated with conventional *vs* atypical antipsychotics. Their results suggest that conventional antipsychotics are at least as likely as the atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning (Wang *et al*., 2005).

These data prompted us to initiate a study in order to assess the tolerability, safety, and clinical benefit of quetiapine in treating elderly AD patients with BPSD in a double-blind, placebo-controlled design.

METHODS

Study design and patients

Patients with AD (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-IV)with BPSD (Finkel, 1996) participated in a 6-week, randomized, double-blind, placebo-controlled trial. The trial was approved by the local Institution Review Board and National Ethical Committee. Patients or their legally authorized representatives provided written informed consent prior to trial entry, after detailed explanation of the study. Inclusion criteria were: age >50 years, dementia of the Alzheimer's type diagnosed according to DSM-IV criteria, Mini-Mental State Examination (MMSE) score <24 and a score >6 on any of the Neuropsychological Inventory (NPI) items. The Exclusion criteria were: other types of dementia (e.g. vascular, frontotemporal lobe dementia), concomitant malignant disease, active ischemic heart disease or chronic heart failure, women of childbearing potential and alcohol or drug abuse.

Treatment

The investigators adjusted daily doses of quetiapine on the basis of clinical response and tolerability. After initial screening visit, patients were given at visit 2 (baseline) quetiapine at a dose of 25 mg BID during the first week, and then increased to a target dose of 150 mg/day by increments of 50 mg every week. If at the target dose no NPI improvement was measured additional increments of 50 mg per week were continued until a maximal dose of 300 mg/day or until side effects were reported by the patient.

No other antipsychotic drugs and anticholinergics were allowed during the trial and for those patients who received other antipsychotics before the trial a wash-out period of 2 weeks was mandatory. Zolpidem in doses up to 10 mg orally was permitted for

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insomnia. Acetylcholinesterase inhibitors (donepezil or rivastigmine) were also permitted if already started before trial entry.

Assessments

The two co-primary measures were the NPI score performed at entry, Weeks 4 and 6 and the Clinical Global Impression of Change (CGI-C) score performed at entry, Weeks 2, 3, 4, 5, 6 and study end or withdrawal, where the primary endpoints were the change from baseline to study end (or withdrawal). Secondary efficacy measures were the MMSE score performed at study entry and end (or withdrawal), the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movement Scale (AIMS) scores both performed at study entry and Weeks 2, 4, 6 and study end. Other measures were: vital signs (pulse and blood pressure [BP]) and ECG at study entry and end, laboratory tests including complete blood count, chemistry, urine analysis, also thyroid function, vitamin B12 and folate levels, at study entry and again upon trial completion (only hematology and chemistry). A complete physical and neurological examination was carried out at study entry and end. Weight was recorded at study entry and end. At each visit patients were questioned regarding side effects and if reported these were recorded on a separate sheet and assessed as related or not to the medication and which measures were taken in consequence. In case serious adverse events (SAE) were recorded Astra Zeneca was to be contacted within 24 h and a SAE report was to be filed.

Sample size calculation and statistical analysis

To detect an average difference of 25% improvement on the NPI score from baseline to 6 weeks between active treatment and placebo with a power of 90% at the 7% (two-sided) level of significance, we needed a sample size of at least 40 (20 in each group).

Demographic factors and clinical characteristics were summarised with counts (percentages) for categorical variables, mean (SD) for normally distributed continuous variables. Comparative analysis was restricted to those patients who had at least one assessment after randomisation. The two-sample *t*-test was applied for testing differences between the study groups for quantitative parameters; the paired *t*-test was applied for testing changes within group. Spearman correlations were applied for testing the correlations between the study parameters examined.

All tests applied were two-tailed, and a *p*-value of 5% or less was considered statistically significant. The data were analyzed using the SAS software (SAS Institute, Cary North Carolina). There was no correction for multiplicity.

For patients who withdrew before Week 6, analyses were performed using observed data and the last observation carried forward (LOCF) method.

RESULTS

Patients and treatment

Forty-four patients with AD and BPSD were screened and 40 patients (26 women), with a mean age of 82.2 (SD 6.4 years) entered the trial. Delusions were the most prevalent symptom, recorded in 30 patients. Twenty-seven patients completed 6 weeks of treatment (Figure 1). Compliance (measured by the number of tablets taken divided by the number of tablets expected to be taken) attained 85% levels. Median total daily dose of quetiapine in the treatment group was 200 mg at Week 6 (range: 75–300 mg/day).

Primary efficacy assessments

Decreases from baseline were observed in NPI total score: 79% in the placebo group and 68.5% in the quetiapine group. No difference was observed when the same NPI items were compared 'head-to-head' between the two groups (Figure 2). The CGI-C score decreased in the quetiapine group ($p = 0.009$) at last visit compared with baseline and did not change significantly in the placebo group ($p = 0.480$; Figure 3).

Patients receiving higher doses of quetiapine (200 or 300 mg/day) showed better improvements on the NPI and CGI-C scales than those on less than 200 mg/day in both arms (see Table 1). A small number of patients in the active arm ($n = 3$) showed a very positive and sustained response to treatment. These patients were younger and had received higher quetiapine doses (300 mg/day).

Thirty-two percent of patients were concomitantly receiving acetylcholinesterase inhibitors (donepezil $n = 8$; rivastigmine $n = 5$) and these drugs did not seem to influence the primary outcome measures in any of the treatment arms.

The MMSE did not change significantly within the two groups ($p = 0.163$ in the placebo and $p = 0.042$ in the quetiapine) and did not differ significantly at study

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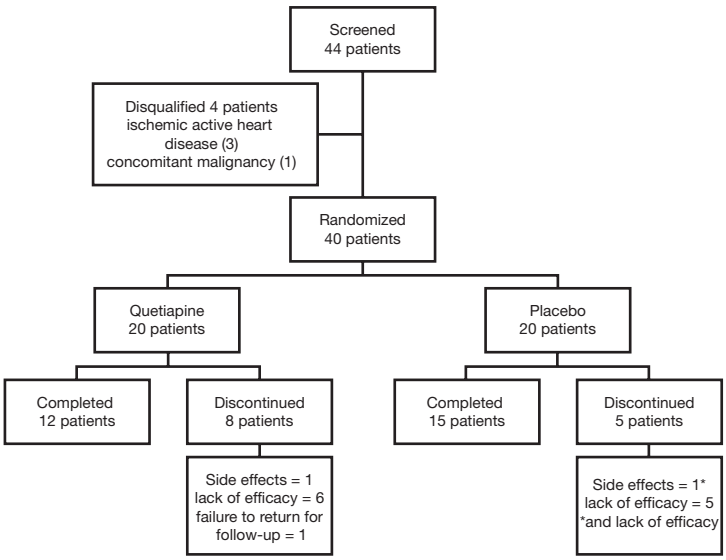
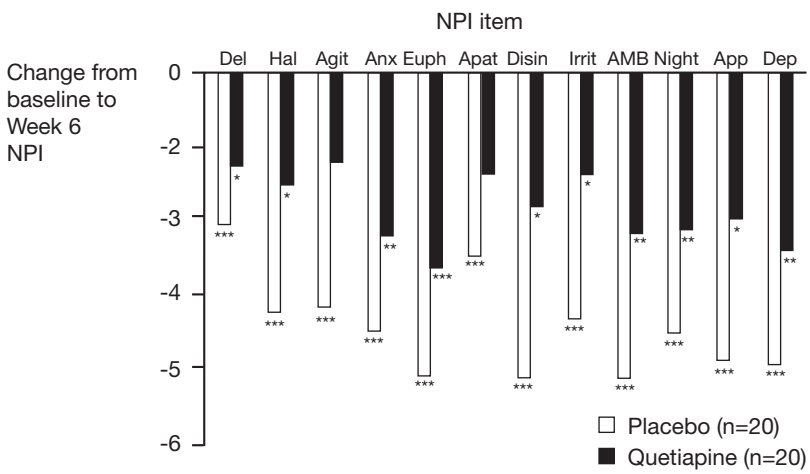


Figure 1. Patient's flow chart.

end between the placebo and quetiapine arms ($p = 0.388$) (Table 2). No significant differences in the AIMS ($p = 0.927$ for quetiapine and $p = 0.331$ for placebo) and SAS scores ($p = 0.665$ for quetiapine and $p = 0.884$ for placebo) were recorded in the two groups and between them ($p = 0.996$ for AIMS, $p = 0.710$ for SAS) at study end (Table 2).

Tolerability

Adverse events (AE's) reported in eight patients (40%) in the placebo arm and five patients (25%) in the quetiapine arm, were minor and did not differ significantly between the two groups (Table 3). Reasons for withdrawal included: lack of efficacy



*p<0.05; **p<0.01; ***p<0.001 vs baseline
Scores on the NPI range from 0 to 12
Agit = agitation; AMB = aberrant motor behavior; Anx = anxiety; Apat, apathy; App = appetite; Del = delusions; Dep = depression; Disin = disinhibition; Euph = Euphoria; Hal = hallucinations; Irrit = irritability; Night = night-time behavior

Figure 2. NPI changes from baseline to Week 6 by treatment group.

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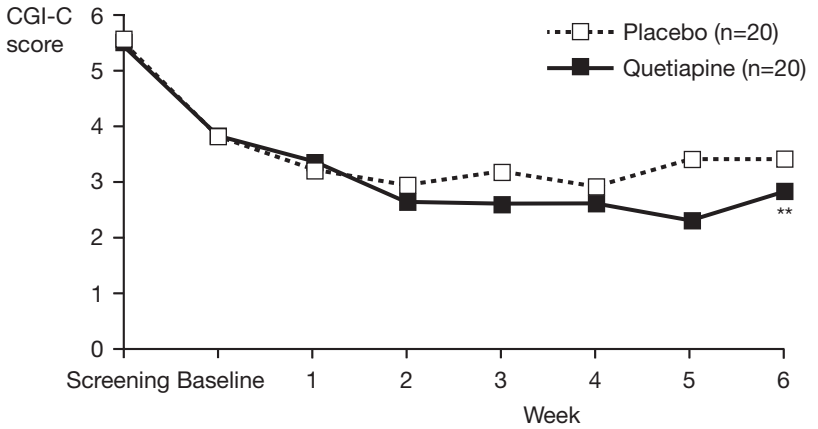

Figure 3. CGI-C scores at screening and from baseline to Week 6 by treatment group.

(six patients in the quetiapine arm and five patients in the placebo arm), adverse events (one patient in each arm) and failure to return for follow-up (one patient in the quetiapine arm). Sedation (one patient in the quetiapine arm), dizziness (one patient in the placebo arm) were rare and did not result in withdrawal from trial. EPS-related AEs (parkinsonism, akathisia, and falls) occurred in 15% of patients, five times more in the placebo arm (see Table 3).

At endpoint (Week 6), mean total score on the Simpson-Angus Scale and AIMS scores were negligible (Table 2). No clinically meaningful changes were reported in hematological, thyroid function, or hepatic function variables. No ECG changes were recorded.

One patient on quetiapine had an elevated systolic blood pressure (190/90) at visit 2 and this was closely monitored during the first 2 weeks of treatment, then antihypertensive therapy was initiated (cilazapril 2.5 mg/day) and the BP normalized. This event was not considered related to quetiapine treatment as the patient complained of headaches before treatment was initiated and they resolved once antihypertensive treatment was started and blood pressure normalized.

No significant weight changes were recorded in either arm. Mean weight at study initiation was 63.97 kg, *vs* mean weight at study end 63.57 kg. A mean weight of 66.45 kg was reported in the quetiapine arm at study initiation and 66.34 kg at study end ($p = 0.98$) and a mean weight of 61.50 kg was reported in the placebo arm at study initiation and 60.62 kg at study end ($p = 0.82$).

DISCUSSION

Quetiapine, a dibenzothiazepine derivative, is a SGA with demonstrated efficacy in schizophrenia and bipolar mania. It was also reported that quetiapine's extrapyramidal side effects are similar to placebo levels (Kivircik *et al*., 2005).

The present prospective double-blind, placebo-controlled study provides some clinical evidence regarding tolerability, safety and clinical response in elderly AD patients with BPSD treated with quetia-

Table 1. Mean age, NPI and CGI per dose categories in men and women

Dose	Mean age, years (number of patients per gender)		NPI		CGI	
<200 mg/day	81 (2F)	80.6 (3M)	−0.78 (2F)	0.16 (3M)	−0.5 (2F)	−1.6 (3M)
200 mg/day	83 (3F)		−0.01 (3F)		−1.6 (3F)	
300 mg/day	85.3 (6F)	80 (6M)	−0.25 (6F)	−0.78 (6M)	−0.6 (6F)	−0.8 (6M)

F = Female; M = Male.

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Table 2. MMSE scores of patients on quetiapine and placebo at baseline and study end, AIMS scores for patients on placebo and quetiapine at baseline and Weeks 2, 4, 6 and SAS scores for patients on placebo and quetiapine at baseline and at Weeks 2, 4, 6 and 8

	Drug									
	Placebo					Quetiapine				
	N	Mean	Std	Min	Max	N	Mean	Std	Min	Max
MMSE										
Baseline	20	14.3	6.8	0.0	23.0	20	14.5	6.3	1.0	24.0
Final	19	14.9	7.3	0.0	26.0	19	13.5	6.8	1.0	24.0
AIMS										
Baseline	20	0.3	1.1	0.0	5.0	18	0.9	22	0.0	6.0
Week 2	19	0.3	1.2	0.0	5.0	17	0.6	1.5	0.0	5.0
Week 4	15	0.3	1.3	0.0	5.0	14	0.5	1.4	0.0	5.0
Week 6	19	0.2	0.9	0.0	4.0	19	0.8	2.2	0.0	8.0
SAS										
Baseline	20	14.2	3.5	9.0	25.0	18	15.8	5.8	7.0	30.3
Week 2	19	14.8	3.7	10.0	25.0	17	15.8	5.0	8.0	29.0
Week 4	15	15.1	3.3	9.0	24.0	13	13.8	3.4	8.0	19.0
Week 6	19	14.4	3.0	9.0	22.0	19	16.1	4.9	8.0	27.0

MMSE maximum score of 30, a score below 26 is considered the cut-off score for cognitive decline, SAS is a ten-item rating scale used to assess neuroleptic-induced parkinsonism, the cut-off score is 0.3, AIMS is a 12-item rating scale used to assess abnormal movements as part of tardive dyskinesia, the results represent a summed value from adding all the components, a score above 0 is abnormal.
AIMS = Abnormal Involuntary Movements Scale; MMSE = Mini-Mental State Examination; SAS = Simpson Angus Scale.

pine for 6 weeks. The two co-primary measures were the NPI (an objective measure of behavior and psychosis as reported by the patient's caregiver and the CGI-C, a more subjective scale also reported by the patient's caregiver). The CGI-C results favored quetiapine, yet the NPI results appeared to favor placebo. In spite of good compliance and a reasonable time to attain treatment effects, head to head NPI items comparisons show quetiapine did not produce more benefit than placebo, making this a basically negative study.

Table 3. Side effects in the two treatment groups

	Placebo	Quetiapine
Akathisia	1	
Parkinsonism	1	1
Tremor	1	
Diarrhea	1	
Dizziness	1	
Dry mouth		1
Edema	1	
Falls	2	
Headaches		1
Sedation		1
Confusion UTI		1
All	8	5

UTI = Urinary Tract Infection.

The nature of cholinergic, dopaminergic, noradrenergic and other neurotransmitter changes in AD are different from the neurochemical changes in schizophrenia. Another important issue is the symptomatological difference between manifestations of psychosis and behavioral disturbances ensuing from psychosis in AD (BPSD) and schizophrenia. As a result, these symptoms of AD might not respond to the same pharmacological interventions, or at least, not in the same manner. The dosing issue is also relevant; we used doses in the lower range (target dose 150 mg/day to a maximum of 300 mg/day) based upon previous reports (Tariot *et al*., 2000; Cheer and Wagstaff, 2004; Schneider *et al*., 2005b), whereas in schizophrenia the reported effective doses are in the range of 400–800 mg/day. The doses were increased slowly (increments of 50 mg/week) as this method (Goldstein, 1999) was shown to prevent emergence of side effects, like sedation. A significant bulk of literature during the past 5 years has dealt with the issue of increased cardiovascular and CVA mortality following treatment with atypical antipsychotics rising concerns about death in this class of medications including the FDA and European warnings. Quetiapine treatment does not appear to have associated cardiovascular or CVA outcomes despite cardiovascular co-morbidities and unrestricted use of concomitant cardiovascular medications in our patients. We conclude this from our study and previous ones: Schneider *et al*. (2005b)

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showed that the relative risk of CVA in a nursing home population treated with atypicals is only 0.50 for quetiapine compared with 2.85 for risperidone, 2.99 for olanzapine, 2.27 for aripiprazole and 1.27 for haloperidol (Schneider *et al*., 2005b).

Another 10-week, double-blind, randomized study of quetiapine in 333 elderly patients with agitation and dementia showed more promising results. Patients were treated with two fixed doses of quetiapine (100 mg/day and 200 mg/day) or placebo. In a pre-planned subanalysis of patients with Alzheimer's disease, there were significant reductions in the Positive and Negative Syndrome Scale-Excitement Component (the primary endpoint) and CGI-C scores with quetiapine 200 mg/day *vs* placebo, but not 100 mg/day *vs* placebo (Zhong *et al*., 2007).

Two recent double-blind, placebo-controlled, parallel design study of quetiapine for hallucinations in PD including 31 subjects with PD and prominent visual hallucinations receiving quetiapine up to 200 mg/day of quetiapine or matching placebo (Ondo *et al*., 2005) and 59 PD with drug induced psychosis titrated to a mean dose of 119 mg (Rabey *et al*., 2007) concluded that there was no significant improvement in psychosis rating compared with placebo. Similar studies in AD (Ballard *et al*., 2005; Tariot *et al*., 2006; Zhong *et al*., 2007) lead to the same conclusion.

Our study included a small sample size and a symptomatically heterogeneous group but larger double-blind, placebo-controlled studies support our findings. The high prevalence and morbidity associated with psychosis in AD warrants the investigation of new pharmacological agents for the treatment of BPSD.

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Preliminary results of the study were presented at the Annual Meeting of the Israeli Neurological Society, 2005 as a poster presentation. The presentation was awarded the best poster prize at the meeting.

REFERENCES

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

Ballard C, Margallo-Lana M, Juszczak E, *et al*. 2005. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ.* **16**: 874. Epub 2005 Feb 18.

Baskys A. 2004. Lewy body dementia: the litmus test for neuroleptic sensitivity and extrapyramidal symptoms. *J Clin Psychiatry* **65** (Suppl 11): 16–122.

Cheer SM, Wagstaff AJ. 2004. Quetiapine: a review of its use in the management of schizophrenia. *CNS Drugs* **18**: 173–199.

Coen RF, Swanwick GRJ, O'Boyle CA, Coakley D. 1997. Behavior disturbances and other predictors of care burden in Alzheimer's disease. *Int J Geriatr Psychiatry* **12**: 331–336.

De Deyn PP, Raberru K, Rasmussen A, *et al*. 1999. A randomized trial of risperidone, placebo and haloperidol for behavioral symptoms of dementia. *Neurology* **53**: 946–955.

Ferris SH, Steinberg G, Shulman E, *et al*. 1987. Institutionalization of Alzheimer's disease patients: reducing precipitating factors through family counseling, Home. *Health Care Serv Q* **8**: 23–51.

Finkel SI. 1996. New focus on behavioural and psychological signs an dsymptoms of dementia. *Int Psychogeriatrics.* **8** (Suppl. 3): 215–216.

Goldstein JM. 1999. Quetiapine fumarate (Seroquel): a new citypical antipsychotic. *Drug Today (Barc)*. **35**(3): 193–210.

Jost BC, Grossberg GT. 1996. The evolution of psychiatric symptoms in Alzheimer's disease: a natural history study. *J Am Geriatr Soc* **44**: 1078–1081.

Kivircik Akdede BB, Alptekin K, Kitis A, Arkar H, Akvardar Y. 2005. Effects of quetiapine on cognitive functions in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **29**(2): 233–238.

Kunik ME, Puryear L, Orongo CA, *et al*. 1998. The efficacy and tolerability of divalproex sodium in elderly demented patients with behavioral disturbances. *Int J Geriatr Psychiatry* **13**: 29–34.

Meltzer HY, McGurck SR. 1999. The effects of clozapine, risperidone and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* **25**: 233–255.

Mintzer JE, Mullen JA, Sweitzer DE. 2004. A comparison of extrapyramidal symptoms in older outpatients treated with quetiapine or risperidone. *Curr Med Res Opin* **20**: 1483–1491.

Oberbolzer AF, Hendriksen C, Monsch AU, *et al*. 1992. Safety and effectiveness of low-dose clozapine in psychogeriatric patients: a preliminary study. *Int Psychogeriatr* **4**: 187–195.

Ondo WG, Tintner R, Dat Voung K, *et al*. 2005. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* **20**: 958–963.

Rabey JM, Prokhorov T, Miniovitz A, *et al*. 2007. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labelled study of 3 months' duration. *Mov Disord* **22**: 313–318.

Reisberg B, Borenstein J, Salob SP, *et al*. 1986. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry* **37**: 1199–1201.

Schneider LS, Dagerman KS, Insel P. 2005a. Risk of death with atypical antipsychotic drug treatment for dementia. *JAMA* **294**: 1934–1943.

Schneider LS, Tariot P, Mintzer J, *et al*. 2005b. Risks for cerebrovascular adverse events: use of quetiapine in patients with dementia, poster presented at the 158th Annual Meeting of the American Psychiatric Association, Atlanta, GA 21-26 May.

Schneider LS, Tariot PN, Dagerman KS, *et al*. the CATIE-AD study group. 2006. Effectiveness of atypical antpsychotic drugs in patients with Alzheimer's disease. *N Engl J Med.* **12**: 1525–1538.

Street JS, Clark WS, Kadam DL, *et al*. 2001. Long term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. *Int J Geriatr Psychiatry* **16**(Suppl 1): S62–S70.

Tariot PN, Profenno LA, Ismail MS. 2004. Efficacy of atypical antipsychotics in elderly patients with dementia. *J Clin Psychiatry* **65** (Suppl 11): 11–15.

Tariot PN, Salzman C, Yeung PP, *et al*. 2000. Long-term use of quetiapine in elderly patients with psychotic disorders. *Clin Ther* **22**: 1068–1084.

Tariot PN, Schneider L, Katz IR, *et al*. 2006. Quetiapine treatment of psychosis associated with dementia: a double blind randomized, placebo controlled clinical trial. *Am J Geriatr Psychiatyr* **14**: 767–776 [Erratum in: *Am J Geriatr Psychiatry.***14**: 998].

Wang PS, Schneeweiss S, Avorn J, *et al*. 2005. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* **353**: 2335–2341.

Zhong K, Tariot P, Minkwitz MC, *et al*. 2007. Quetiapine to treat agitation in dementia: a randomized, double blind placebo controlled study. *Curr Alzheimer Res* **4**: 81–93.

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