Treatment of behavioural, cognitive and circadian rest-activity cycle disturbances in Alzheimer's disease: haloperidol vs. quetiapine

Savaskan, E; Schnitzler, C; Schröder, C; Cajochen, C; Müller-Spahn, F; Wirz-Justice, A

Postprint available at:
http://www.zora.uzh.ch

Posted at the Zurich Open Repository and Archive, University of Zurich.
http://www.zora.uzh.ch

Originally published at:
Treatment of behavioural, cognitive and circadian rest-activity cycle disturbances in Alzheimer's disease: haloperidol vs. quetiapine

Abstract

This 5-wk, open-label, comparative study investigated the effects of quetiapine and haloperidol on behavioural, cognitive and circadian rest-activity cycle disturbances in patients with Alzheimer's disease (AD). Out of a total of 30 patients enrolled in the study, there were 22 completers, 11 in the quetiapine group (mean age 81.9 +/- 1.8 yr, mean baseline MMSE 19.9 +/- 1.3, mean dose 125 mg) and 11 in the haloperidol group (mean age 82.3 +/- 2.5 yr, mean baseline MMSE 18.1 +/- 1.3, mean dose 1.9 mg). As shown in the Neuropsychiatric Inventory, both medications reduced delusion and agitation, whereas quetiapine additionally improved depression and anxiety. Haloperidol worsened aberrant motor behaviour and caused extrapyramidal symptoms. In the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery which assessed cognitive parameters, quetiapine improved word recall; significant interaction terms revealed differences between quetiapine and haloperidol in word-list memory and constructional praxis. According to the Nurses' Observation Scale for Geriatric Patients (NOSGER) quetiapine improved instrumental activities of daily living. Actimetry documented the circadian rest-activity cycle before and after treatment. Sleep analysis revealed that patients receiving quetiapine had shorter wake bouts during the night, whereas patients receiving haloperidol had fewer though longer immobile phases. The study provides evidence that quetiapine at a moderate dose may be efficacious in treating behavioural disturbances in AD, with better tolerability than haloperidol.
Treatment of behavioural, cognitive and circadian rest-activity cycle disturbances in Alzheimer’s disease: haloperidol vs. quetiapine

Egemen Savaskan¹, Corina Schnitzler², Carmen Schröder², Christian Cajochen², Franz Müller-Spahn¹ and Anna Wirz-Justice²

¹ Geriatric Psychiatry and ² Centre for Chronobiology, University Psychiatric Hospitals, CH-4025 Basel, Switzerland

Abstract

This 5-wk, open-label, comparative study investigated the effects of quetiapine and haloperidol on behavioural, cognitive and circadian rest-activity cycle disturbances in patients with Alzheimer’s disease (AD). Out of a total of 30 patients enrolled in the study, there were 22 completers, 11 in the quetiapine group (mean age 81.9 ± 1.8 yr, mean baseline MMSE 19.9 ± 1.3, mean dose 125 mg) and 11 in the haloperidol group (mean age 82.3 ± 2.5 yr, mean baseline MMSE 18.1 ± 1.3, mean dose 1.9 mg). As shown in the Neuropsychiatric Inventory, both medications reduced delusion and agitation, whereas quetiapine additionally improved depression and anxiety. Haloperidol worsened aberrant motor behaviour and caused extrapyramidal symptoms. In the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropsychological test battery which assessed cognitive parameters, quetiapine improved word recall; significant interaction terms revealed differences between quetiapine and haloperidol in word-list memory and constructional praxis. According to the Nurses’ Observation Scale for Geriatric Patients (NOSGER) quetiapine improved instrumental activities of daily living. Actimetry documented the circadian rest-activity cycle before and after treatment. Sleep analysis revealed that patients receiving quetiapine had shorter wake bouts during the night, whereas patients receiving haloperidol had fewer though longer immobile phases. The study provides evidence that quetiapine at a moderate dose may be efficacious in treating behavioural disturbances in AD, with better tolerability than haloperidol.

Received 12 April 2005; Reviewed 29 May 2005; Revised 4 July 2005; Accepted 7 July 2005; First published online 5 September 2005

Key words: Actimetry, Alzheimer’s disease, behavioural symptoms, haloperidol, quetiapine.

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly population, causing progressive cognitive decline often accompanied by affective, behavioural and circadian sleep-wake cycle disturbances. These can be manifested as agitation, aggression, purposeless activity, wandering, pacing, nocturnal restlessness, depressive features and psychotic symptoms such as hallucinations and delusions (Van Someren et al., 1996; Vitiello and Borson, 2001). At least one of these neuropsychiatric disturbances is found in 60% of AD patients (Lyketsos et al., 2000). The behavioural and sleep-wake cycle disturbances of AD have a severe impact on the patient’s and caregiver’s quality of life, often being the reason for the decision to institutionalize these patients (Pollak and Stokes, 1997). Therefore, effective treatment of these symptoms may help to reduce social and economic costs. Unfortunately, most of the agents used in this polymorbid population, such as benzodiazepines, anxiolytics or anticonvulsants cause severe side-effects and interact with internistic diseases also present, as well as with other medication.

Neuroleptics are commonly used to treat behavioural symptoms in AD patients (Motsinger et al., 2003; Profenno and Tariot, 2004; Salzman, 2001). However, because of their anticholinergic side-effects and tendency to induce extrapyramidal symptoms (EPS), classical neuroleptics are disadvantageous and atypical neuroleptics are receiving more attention in the management of these behavioural disturbances. In a previous single case study, we showed that...
haloperidol, a conventional neuroleptic, disrupted the circadian rest-activity cycle of an early-onset AD patient, whereas clozapine improved it (Wirz-Justice et al., 2000).

Quetiapine (Seroquel®), a new atypical neuroleptic, is a dibenzothiazine derivative that has been evaluated for the treatment of patients with psychotic symptoms (DeVane and Nemeroff, 2001). It exhibits strong binding properties for serotonin 5-HT₂A, histamine H₁ and α₁ adrenergic receptors, some α₂ adrenergic receptor-blocking qualities, but markedly low affinity to dopamine D₂ and D₄ receptors when compared with classical antipsychotic agents (Richelson and Souder, 2000; Saller and Salama, 1993). In addition, as shown by electrophysiological studies, it has high selectivity for mesolimbic dopamine receptors (Saller and Salama, 1993). The weak anti-cholinergic effects and low incidence of EPS after quetiapine have been postulated to be related to this receptor-binding profile, and would thus be advantageous for treating patients with impaired cholinergic function such as present in AD (Tariot and Ismail, 2002).

Quetiapine has been found to be both effective and well tolerated in elderly patients with AD (Fujikawa et al., 2004; Salzman, 2001; Scharre and Chang, 2002; Tariot and Ismail, 2002; Tariot et al., 2000), as well as being effective in treating psychotic symptoms and disruptive behaviour in other causes of dementia, for example in Lewy body dementia (LBD) (Davis and Baskys, 2002; Fernandez et al., 1999, 2002, 2003; Takahashi et al., 2003). In AD, an 8-wk treatment of behavioural symptoms with quetiapine significantly improved agitation, delusions, activity disturbances, aggressiveness and diurnal rhythm disturbances (Fujikawa et al., 2004). Quetiapine does not appear to worsen cognition (Scharre and Chang, 2002), this being an additional limiting factor for the use of classical neuroleptics in a cognitively disabled population. The aim of the present study was the comparative evaluation of quetiapine and haloperidol effects on behavioural and cognitive symptoms in AD patients. In addition, actimetry was carried out to detect possible differential neuroleptic modification of the circadian sleep–wake cycle disturbances.

**Method**

**Study design**

The present study was a 5-wk, single centre, comparative, randomized, open-label trial to assess the improvement of behavioural symptoms, cognitive state and the circadian rest–activity cycle in AD patients treated with either quetiapine or haloperidol. The protocol was approved by the local Ethical Committee. Full and adequate oral and written information about objectives and goals of the study, possible therapeutic advantages and side-effects was given to the subjects and their caregivers. After informed consent and a maximum 7 d run-in period for baseline assessments, eligible subjects diagnosed as probable AD patients with behavioural symptoms were randomized to one of the two treatment groups. Screening and demographic measurements included: date of birth, sex, race, weight, height, tobacco and alcohol consumption, significant medical and surgical history, physical and laboratory examination, electrocardiogram and the diagnosis of AD according to the criteria of ICD-10.

The inclusion criteria included confirmed diagnosis of AD, behavioural symptoms (at least three of the following: aggression, psychotic symptoms, sleep–wake cycle disturbances, agitation, restlessess or sundowning), permanent medical or social care available during the study, written informed consent and age over 65 yr. The exclusion criteria included known sensitivity to study drugs, evidence of chronic and/or severe renal, hepatic, cardiovascular, pulmonary or gastrointestinal impairment or cancer, other antipsychotic medication than the study drugs, participation in any other drug trial and contraindications as detailed in the country-specific prescribing information for the study drugs. Subjects were free to withdraw their informed consent at any time, without prejudice to further treatment.

Patient data was collected during three visits: Visit 1 during the run-in period for baseline assessments; Visit 2, 1 d prior to commencing study drugs and Visit 3 at the end of the fifth week of treatment. During the treatment period the patients received either quetiapine (25–200 mg) or haloperidol (0.5–4 mg), and no other neuroleptic. Initial dosage was 25 mg for quetiapine and 0.5 mg for haloperidol. The dosage was increased weekly by 25 mg for quetiapine and 0.5 mg for haloperidol. All other concomitant medication was continued and was documented. All AD patients received a cholinesterase inhibitor as co-medication (galantamine 2 × 8 mg). The protocol was planned in 2001 and patients entered the study from 2002 to 2004.

**Patients**

Thirty AD in-patients hospitalized on the gerontopsychiatric ward entered the study. No patients
had any prior history of psychiatric diagnosis. Four patients dropped out in the course of the study. Owing to an unforeseen rater change, the last four patients were not included in the analysis. Thus, a total of 22 AD patients finished the 5-wk treatment period and could be evaluated: 11 in the haloperidol group (Table 1: 6 females and 5 males, mean age (±S.E.M.) 82.3±2.5 yr; mean baseline MMSE 18.1±1.3; mean dose at the end of the study 1.9 mg; starting dose 0.5–1 mg) and 11 in the quetiapine group (Table 1: 9 females and 2 males, mean age 81.9±1.8 yr; mean baseline MMSE 19.9±1.3; mean dose at the end of the study 125 mg; starting dose 25 mg).

Psychometric test battery

The following test battery was used twice, at baseline and at the end of the 5-wk treatment period (Visits 1 and 3), to assess behavioural and cognitive symptoms and activities of daily living.

**Neuropsychiatric Inventory (NPI)**

The NPI is a brief interview assessing behavioural disturbances (subscales: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy and aberrant motor behaviour) in dementia (Cummings et al., 1994). The Nursing Home version was used in the present study to assess two additional subscales: appetite and night-time behavioural disturbances. Each subscale consists of a frequency rating (1–4) and a severity rating (1–3), and the subscale score is the product of the frequency x the severity (raw score) for each domain. Concurrent reliability has been determined by comparing the NPI subscale with subscales of the BEHAVE-D and the Hamilton Depression Rating Scale. Highly significant correlations were found. The NPI is thus a suitable test battery for assessing behavioural symptoms in AD (Cummings et al., 1994). For each symptom subscale the difference from

---

**Table 1. Demographic data and outcome measures of behavioural and cognitive assessments of 22 AD patients who finished the 5-wk treatment period with haloperidol or quetiapine**

<table>
<thead>
<tr>
<th>Case</th>
<th>Max. dose</th>
<th>Sex</th>
<th>Age</th>
<th>NPI Baseline</th>
<th>NPI Week 5</th>
<th>MMSE Baseline</th>
<th>MMSE Week 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 mg</td>
<td>M</td>
<td>84</td>
<td>37</td>
<td>38</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>2 mg</td>
<td>F</td>
<td>85</td>
<td>43</td>
<td>0</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>1.5 mg</td>
<td>F</td>
<td>68</td>
<td>23</td>
<td>42</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>4 mg</td>
<td>M</td>
<td>79</td>
<td>18</td>
<td>45</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>1.5 mg</td>
<td>F</td>
<td>81</td>
<td>36</td>
<td>35</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>2 mg</td>
<td>F</td>
<td>94</td>
<td>11</td>
<td>40</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>2 mg</td>
<td>F</td>
<td>91</td>
<td>50</td>
<td>36</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>1.5 mg</td>
<td>F</td>
<td>71</td>
<td>11</td>
<td>11</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>1.5 mg</td>
<td>M</td>
<td>90</td>
<td>22</td>
<td>5</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>2 mg</td>
<td>M</td>
<td>77</td>
<td>32</td>
<td>31</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>1.5 mg</td>
<td>M</td>
<td>85</td>
<td>10</td>
<td>21</td>
<td>26</td>
<td>28</td>
</tr>
</tbody>
</table>

| Quetiapine | | | | | | | |
| 1 | 125 mg | F | 77 | 31 | 3 | 15 | 26 |
| 2 | 175 mg | F | 83 | 44 | 69 | 12 | 9 |
| 3 | 75 mg | M | 89 | 22 | 20 | 26 | 25 |
| 4 | 150 mg | F | 78 | 41 | 7 | 20 | 19 |
| 5 | 200 mg | F | 70 | 53 | 32 | 17 | 22 |
| 6 | 125 mg | F | 80 | 18 | 9 | 25 | 28 |
| 7 | 225 mg | F | 80 | 36 | 5 | 24 | 26 |
| 8 | 75 mg | F | 89 | 34 | 15 | 23 | 23 |
| 9 | 125 mg | M | 79 | 29 | 0 | 22 | 25 |
| 10 | 75 mg | M | 87 | 51 | 7 | 18 | 18 |
| 11 | 25 mg | F | 89 | 16 | 2 | 17 | 23 |

M, male; F, female; NPI, Neuropsychiatric Inventory (total score of all subscales, each frequency times the severity); MMSE, Mini-Mental State Examination.
baseline to post-testing was calculated with raw scores.

**Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropsychological test battery**

CERAD, established in 1986 by the National Institute of Aging, developed a battery of standardized instruments for the evaluation of AD patients (Heyman et al., 1990; Morris et al., 1988). Three primary assessments include a clinical battery, a neuropsychological battery and a neuropathological assessment. The neuropsychological battery used in the present study to assess cognition included the following tests: verbal fluency, modified Boston Naming Test, Mini-Mental State Examination (MMSE), constructional praxis and recall, word-list memory, word-list recognition and recall.

**Nurses’ Observation Scale for Geriatric Patients (NOSGER)**

NOSGER is an assessment scale for behaviour and functioning in elderly patients (Spiegel et al., 1991). It has 30 items coinciding with one of the following six assessment areas: memory, instrumental activities of daily living, social behaviour, self-care, mood and disturbing behaviour.

**Actimetry**

To investigate the circadian rest–activity cycle, the patients were asked to wear a small activity monitor (Actiwatch-L®, Cambridge Neurotechnology Ltd, Cambridge, UK) on the non-dominant wrist continuously for 7 consecutive days, twice, prior to the start of neuroleptic medication and during week 5 of treatment. Actimetry in patients with AD has been approved by the Ethical Committee of the Department of Medicine, University Hospital Basel, and has been successfully employed in our previous clinical trials (Fontana-Gasio et al., 2003; Werth et al., 2002; Wirz-Justice et al., 2000). The actigraph measures locomotor activity by a piezoelectric element and activity counts are accumulated in 1-min epochs. Concurrent with activity monitoring, light exposure is measured by an implemented light sensor. This non-invasive method allows patients to continue their daily activities and choose their own bedtimes.

**Actimetry data analysis**

The detailed data analysis procedure has been previously reported (Werth et al., 2002). Patients’ raw motor activity was documented as consecutive daily activity plots. After checking for artefacts and removing/interpolating missing data, mean values for selected time episodes were analysed as 24-h patterns to compare changes in the rest–activity cycle longitudinally. Sleepwatch® software (Sleep Analysis Software version 4.12; Cambridge Neurotechnology, Cambridge, UK) provides estimates of ‘sleep’ from the rest–activity cycle data (with reasonable validation when compared with polysomnography). The following variables from the activity data of the selected time segments were extracted: mean diurnal (=daytime episode between lights on and lights off), nocturnal (=night-time episode between lights off and lights on), and 24-h activity; total wakefulness during the sleep period; total sleep during the wake period and number of nocturnal wake bouts. Sensitive variables that quantify the circadian rhythm aspects of the activity pattern were also extracted: (1) inter-daily stability gives an indication of the degree of synchronization of the rest–activity cycle to environmental timing cues; (2) intra-daily variability is a measure of the fragmentation of the rest–activity cycle; (3) relative amplitude is the difference between the most active 10 h during the day and the least active 5 h during the night.

**Statistics**

Changes over time in the variables described above were analysed using analysis of variance for repeated measures (ANOVA) followed by Duncan’s multiple-range tests when the interaction term of the ANOVA was significant.

**Results**

Patients’ demographic data and the results of NPI and MMSE assessments are summarized in Table 1. In each group two dropouts were registered because of adverse events or coincidental diseases: in the haloperidol group one patient discontinued the study because of EPS and one patient because of a transient ischaemic attack; in the quetiapine group one patient dropped out because of postural hypotonia and one because of myocardial infarction, early in the second week of the treatment period, which might be not related to the treatment. The otherwise observed adverse events were: in the haloperidol group, two patients had EPS (Table 1, cases 2 and 11), one patient had an infection of unknown origin (Table 1, case 1) and one patient showed arterial hypertonia (Table 1, case 3); in the quetiapine group one patient showed reversible syncope (Table 1, case 2) and one patient had gastroenteritis (Table 1, case 7).
Analysis of NPI scores, which assessed the behavioural effects of treatment revealed similar effects both for haloperidol and quetiapine in two subscales: both medications reduced delusions ($p = 0.017$ vs. baseline (main effect); agitation: ** $p = 0.016$ vs. baseline (main effect); depression: *** $p = 0.031$ quetiapine vs. baseline (post-hoc analysis); anxiety: $p = 0.052$ quetiapine vs. baseline (post-hoc analysis); abnormal motor behaviour: $p = 0.035$ haloperidol vs. baseline (post-hoc analysis).

In the CERAD, assessing the cognitive parameters, both haloperidol and quetiapine were effective in improving word recall ($p = 0.031$, main effect) (Figure 2). Significant interaction terms revealed differences between quetiapine and haloperidol in word-list memory ($p = 0.03$), and constructional praxis ($p = 0.038$) (Figure 3a, b). Post-hoc analyses showed that quetiapine significantly improved word-list memory ($p = 0.006$) relative to baseline (Figure 3a). Interestingly, at the end of the 5-wk treatment, quetiapine-treated patients showed a non-significant 2-point improvement in the mean MMSE score when compared with baseline (baseline: $19.9 \pm 1.3$; end of week 5: $22.2 \pm 1.6$; Table 1, Figure 2).

In NOSGER the significant interaction term ($p = 0.04$) revealed differences between quetiapine and haloperidol treatments: post-hoc analysis demonstrated that quetiapine improved instrumental activities of daily living in AD patients (Figure 3c).

Actimetry revealed what the clinical observation suggested that these hospitalized AD patients have highly disturbed sleep–wake cycles. No drug effects on the circadian rest–activity cycle were found. However, in the sleep analysis, quetiapine or haloperidol treatment differentially effected sleep consolidation as shown by the actimetry data: quetiapine improved sleep patterns in AD patients, with patients experiencing shorter wake bouts ($p = 0.023$) at the end of week 5 compared with baseline (Figure 4a) indicating a more consolidated sleep episode. Patients in the haloperidol-treatment group showed a different effect, of fewer ($p = 0.053$) though longer ($p = 0.01$) immobile phases during sleep compared with baseline (Figure 4b, c).

**Discussion**

The present study revealed that quetiapine was superior to haloperidol in controlling behavioural, cognitive and circadian rest–activity cycle disturbances.
in AD patients. Whereas both quetiapine and haloperidol were effective in reducing delusions and agitation (NPI), quetiapine additionally improved depression and anxiety. The cognitive advantages of quetiapine may be reflected in the improvement of word-list memory and word recall in the CERAD, as well as the lack of worsening in the MMSE over this time period. These individual effects of quetiapine probably contributed to an improvement in the activities of daily living (NOSGER). Finally, the actimetry data revealed that quetiapine treatment resulted in more consolidated night-time sleep.

Adverse events observed in the study patients were EPS, infection and arterial hypertonia in the haloperidol group and, syncope and gastroenteritis in the quetiapine group. Whereas infectious diseases may not reflect medication-related side-effects, we should pay attention to EPS and syncope. Two patients in the haloperidol group showed EPS, in accordance with previous data revealing EPS as a common side-effect of haloperidol treatment in AD patients, whereas quetiapine-treated patients experience significantly fewer EPS (Tariot and Ismail, 2002; Tariot et al., 2000). Thus, the worsening in the NPI subscale – aberrant motor behaviour – in the

Figure 2. Effect of quetiapine (□) and haloperidol (■) on cognitive performance in CERAD scores. Word-list recall: * p = 0.031 vs. baseline (main effect); word-list memory: ** p = 0.006 quetiapine vs. baseline (post-hoc analysis).

Figure 3. Effect of quetiapine and haloperidol on (a) word-list memory, and (b) constructional praxis in CERAD at baseline and at the end of the fifth treatment week. (c) Effect of quetiapine and haloperidol on instrumental activities of daily living in NOSGER.

Figure 4. Actimetry data: effect of quetiapine and haloperidol on (a) mean wake bout time, (b) number of immobile phases, and (c) mean length immobile.
haloperidol group may underline haloperidol’s negative effects on motor symptoms.

Because of its effect on improving psychosis without exacerbating movement disorders, quetiapine has been recommended for treatment of psychotic symptoms in patients with LBD (Davis and Baskys, 2002; Fernandez et al., 1999). Quetiapine has also been used for the treatment of behavioural and psychotic symptoms in patients with LBD with no significant changes in EPS (Davis and Baskys, 2002; Takahashi et al., 2003). The most common side-effects of quetiapine noted in the elderly have been somnolence (30%), dizziness (17%), and postural hypotension (15%) (Tariot et al., 2000). Syncope was an adverse event in one patient in the quetiapine treatment group in our study, probably due to postural hypotension. In the quetiapine group one patient dropped out because of myocardial infarction very early in the treatment phase, which is unlikely to be related to treatment. Nevertheless, an excess of cerebrovascular and cardiovascular events has been reported with other antipsychotics other than quetiapine (Lee et al., 2004). Although several cerebrovascular risk factors present in AD patients have been found to predispose to cerebrovascular events and have to be taken in consideration when prescribing antipsychotics, presently can it not be excluded that this is a class effect which is not constrained to the three drugs that have been studied in this respect so far.

To avoid side-effects, quetiapine has been recommended to be initiated at a very low dose of 25 mg (McManus et al., 1999), or even 12.5 mg (Motsinger et al., 2003), and to be increased slowly. The starting dose in our study was 25 mg which may account for the low incidence of side-effects. The optimal quetiapine dose for AD patients has been suggested to vary between 25 and 200 mg/d (Sultzer, 2004), and the mean dose of 125 mg attained in the present study is comparable with analogous studies in the literature (Tariot et al., 2000). The patient showing syncope as an adverse event (Table 1, case 2, 175 mg) was one of the four cases receiving quetiapine doses greater than the mean dose (Table 1, cases 2, 4, 5 and 7) which again may point to the necessity of careful dosage in this patient group.

Both quetiapine and haloperidol were effective in reducing delusions and agitation, whereas additional positive effects on depression and anxiety were observed in the quetiapine-treated AD patients. The effects of quetiapine to improve psychotic symptoms, aggression and agitation have been well documented in LBD (Davis and Baskys, 2002; Fernandez et al., 1999, 2002, 2003; Takahashi et al., 2003). In an open-label, multicentre trial in 184 elderly patients with psychotic symptoms (43% with AD), quetiapine showed significant improvement in the Brief Psychiatric Rating Scale (BPRS) total score and the Clinical Global Impressions severity of illness item score (Tariot et al., 2000). The same authors also reported a double-blind, placebo-controlled, 10-wk, randomized trial in 284 AD patients with flexible dosing of quetiapine or haloperidol (Tariot and Ismail, 2002). Whereas both quetiapine and haloperidol treatment significantly improved agitation, patients in the quetiapine group had also significantly better functional status as assessed by the BPRS anergia factor, the Physical Self-Maintenance Scale, and the Multidimensional Observation Scale for Elderly Subjects (Tariot and Ismail, 2002). Finally, in an open-label, 12-wk study in AD patients receiving doses from 50 to 150 mg, quetiapine significantly decreased delusions, aggression, and overall behaviours based on NPI scores (Scharre and Chang, 2002). These previous findings support our results that quetiapine is effective in the treatment of psychotic and behavioural symptoms in AD. Although there is still limited evidence, additional data from a Cochrane-based review evaluating the effects of atypical antipsychotics (risperidone and olanzapine) on behavioural symptoms in dementia in randomized trials concluded that atypical antipsychotics in general improve efficacy and adverse-event profiles compared with typical antipsychotic drugs (Lee et al., 2004). Treatment with atypical antipsychotic drugs was superior to placebo for the primary end-point in three of the five trials. However, adverse events were common and included EPS, somnolence, and abnormal gait (Lee et al., 2004).

Our results showed additional quetiapine effects on affective symptoms, improving depression and anxiety in AD. Quetiapine has been found to be a useful agent in the management of depressive symptoms in psychosis (Sajatovic et al., 2002), and in mood disorders including bipolar and schizoaffective disorders (Sajatovic et al., 2001). Thus, because of its sedative effects, quetiapine has been recommended for the treatment of therapy-resistant bipolar disorder (Ghaemi and Katzow, 1999). Nevertheless, it has to be taken in consideration that atypical neuroleptics can, as a rare side-effect, also induce mania (Fahy and Fahy, 2000).

The positive effects of quetiapine treatment on cognitive parameters in our AD patients are in accordance with previous data showing that quetiapine, relative to haloperidol, has a positive impact on cognitive performance in schizophrenia patients...
through the 5-HT binding profile, atypical antipsychotics like quetiapine may also be a consequence of the improvement in behavioural and circadian rest–activity cycle symptoms. Nevertheless, because of their 5-HT receptor-blocking profile, atypical antipsychotics like quetiapine have been shown to have a positive impact on cognition (Tyson et al., 2004). After a 6-wk quetiapine treatment period patients with schizophrenia showed a beneficial influence on auditory short-term memory and recognition memory for patterns and spatial information (Tyson et al., 2004). In schizophrenia patients, the improvement in cognitive parameters have been found not to be attributable solely to changes in positive symptoms of psychosis, negative symptoms, side-effects, or to additional medication use, but rather to be a direct effect of quetiapine (Velligan et al., 2002). However, the positive effect on cognition was found for the high-dose quetiapine treatment with 600 mg/d, and not for the low-dose 300 mg/d treatment group. Since a relatively low quetiapine dose was used in our study and the treatment period was relatively short, the effect on cognitive parameters may also be a consequence of the improvement in behavioural and circadian rest–activity cycle symptoms. Nevertheless, because of their 5-HT receptor-binding profile, atypical antipsychotics like quetiapine have been shown to have a positive impact on cognition (Tyson et al., 2004). After a 6-wk quetiapine treatment period patients with schizophrenia showed a beneficial influence on auditory short-term memory and recognition memory for patterns and spatial information (Tyson et al., 2004). In addition, the thinking time in planning tasks over repeated testing was decreased. The authors suggested that the action through the 5-HT receptor may change dopamine levels in the prefrontal cortex which may be responsible for cognitive effects.

The sleep–wake cycle in these elderly AD patients was highly disturbed. Thus, at this late stage of the disease one can not expect major improvements by any treatment. Nonetheless, actimetry analyses revealed that AD patients receiving quetiapine had a more consolidated sleep phase with shorter wake bouts. The sleep-promoting effects of quetiapine are well documented polysomnographically in schizophrenia patients showing that quetiapine significantly improved sleep induction and continuity under standard and acoustic stress conditions (Cohrs et al., 2004). Increases in total sleep time, sleep efficiency, percentage sleep stage 2 and subjective sleep quality were observed by polysomnographic sleep recording (Cohrs et al., 2004). These sleep-inducing and sleep-modifying effects have been postulated to be related to quetiapine’s antihistaminergic, antidopaminergic and antiadrenergic properties. Whereas some of the observed effects of quetiapine on sleep, such as the increased total sleep time and transient reduction in REM sleep have been postulated to be related to its antihistaminergic effects, the dopamine D2 receptor-blocking qualities of quetiapine have been postulated to be responsible for its sleep-inducing properties (Cohrs et al., 2004).

In contrast, patients in the haloperidol treatment group showed a decrease in the number of immobile phases. These disruptive effects on sleep are in line with our previous findings in AD where haloperidol was shown to induce disruption of the circadian rest–activity cycle parallel to worsening of cognitive state (Wirz-Justice et al., 2000), indicating that classical neuroleptics may aggravate sleep disturbances and not be favourable in AD patients.

In conclusion, quetiapine was effective in treating behavioural and sleep disturbances in AD patients, thus improving cognitive state. Nevertheless, the limitation of small sample size in the present study requires larger double-blind trials to confirm the preliminary results presented here. In addition, the use of neuroleptics in this handicapped population requires the detailed and individual consideration of dosage, possible side-effects and interactions with concomitant medication and diseases.

Acknowledgements

C. Schnitzler and C. Schröder were supported by a grant from AstraZeneca (Switzerland), C. Cajochen by a Swiss National Science Foundation Research Professorship (SNF grants START no. 3130-054991 and no. 3100-055385.98).

Statement of Interest

None.

References


