Quetiapine for Patients with Agitation or Psychosis Related to Alzheimer’s Disease and Vascular Dementia

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Abstract

Objectives: More and more elderly people around the world suffer from dementia and its related behavioral and psychological symptoms. Second generation antipsychotic agents, including quetiapine, are frequently used for patients with dementia-associated agitation or psychosis. However, existing data about effective dose of antipsychotics are mostly drawn from researches focusing on Caucasian patients with Alzheimer’s disease (AD). We accordingly conducted a retrospective study via chart review in a medical center in Taiwan to find out the optimal dose of quetiapine for outpatients with agitation or psychosis related to AD or vascular dementia (VaD).

Methods: Lists of candidate patients were retrieved from the database of a medical center in Taiwan based on their ICD-9 codes and prescription records of antipsychotics obtained from the center’s neurology or psychiatry departments during 2006 and 2007. The candidate patients’ medical charts were then reviewed, and their data entered into final analysis when the following inclusion criteria were met: (1). diagnosis of AD or VaD; (2). prescription of quetiapine exclusively for agitation or psychosis related to dementia; and (3). achievement of “stable state” defined as a period when a constant dose of quetiapine had been maintained for at least 4 weeks during which there had been at least two visits at an interval of more than four weeks. The constant dose during stable state was defined as the “optimal dose” in this study. Optimal doses of the AD group and VaD group were calculated and compared with each other. The relationships between optimal dose and clinical correlates within each group were examined.

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**Results:** A total of 118 patients (75 females, mean [SD] age 77.8 [7.3] years) was included. Forty-nine patients had AD and 69 had VaD. The demographic data and clinical correlates were similar between the two groups, except that more patients with AD took cognitive enhancers. The mean daily optimal dose of quetiapine was not significantly different between the AD patients (38.5 [37.8] mg) and their VaD counterparts (45.7 [69.9] mg). Patients with greater severity required significantly higher dose of quetiapine. Age, gender or symptom profiles were not significantly associated with optimal dose in either group.

**Conclusion:** For patients with VaD related agitation or psychosis, the daily optimal dose was similar to that of patients with AD. Compared to previous studies regarding Caucasian patients, our data showed a relatively lower optimal daily dose of quetiapine for dementia-related psychosis or agitation in Chinese/Taiwanese patients.

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**Key words:** dementia, quetiapine, antipsychotic agent, vascular dementia, Alzheimer’s disease

**Introduction**

It was estimated that the prevalence rate of dementia throughout the world was 3.9% among people older than 60 years, and the annual incidence rate read 7.5 per 1000 populations [1]. Behavioral and psychological symptoms of dementia (BPSD) result in the increase of disability, caregiver stress, institutionalization rate and medical expenditure. Among the variable BPSD, psychosis and agitation are present in more than half of the patients with Alzheimer’s disease (AD) and other dementias [2-4]. A systematic literature review found delusions occurring in 30% to 60% of Taiwanese AD patients, hallucinations in 21% to 26%, and agitation/aggression in 39% to 57% [5].

Antipsychotic agents are widely used to treat dementia-related agitation or psychosis. An expert panel recommended antipsychotic agents as the first-line pharmacotherapy for agitated dementia with delusions and the high-second line for agitated dementia without delusions [6]. Meta-analysis of placebo-controlled, double-blind, parallel-group trials showed nonsignificant or modest effects of second-generation antipsychotics (SGA) to treat delusions, aggression, and agitation in patients with AD or other dementias [7]. Compared with first-generation antipsychotics (FGA), SGA is preferred for its more
tolerable side effect profile, especially for elderly patients [6-9]. Recently, both FGA and SGA were found to be associated with elevated risk of cerebrovascular adverse events and mortality in treating elderly patients with dementia [7, 10-13]. Lowest effective dose of antipsychotic agents with minimal side effects is thus desired, and frequent trials of tapering or withdrawing the medications are necessary. Despite increasing amounts of clinical trials focusing on adequate dose of antipsychotics for BPSD, only few of them were based on Chinese patients.

Quetiapine is a type of SGA suggested to be particularly advantageous for the elderly due to minimal anticholinergic activity, relatively loose binding to dopamine receptors and less extrapyramidal symptoms [14]. Quetiapine was shown to be effective in treating dementia-related behavioral symptoms [15, 16], and some studies found favorable tolerability and side effect profile despite lack of significant efficacy [17-19]. None of these trials, however, were focused on patients with VaD. We therefore conducted a retrospective study based on medical chart review to determine the optimal dose of quetiapine for Taiwanese patients with agitation or psychosis related to both AD and VaD.

**Patient Selection**

The first step aimed to select candidate patients from the database of a medical center in Taiwan according to two criteria: (1). ICD-9 codes 290.0 – 290.4, 294.1 or 331.0; and (2). medications with antipsychotic agents prescribed from neurology or psychiatry departments during 2006 and 2007.

Eligibility of candidate patients was further evaluated through medical charts review by four senior psychiatric residents. To be included, a candidate patient must be diagnosed as having AD or VaD by a neurologist or psychiatrist. Eligible patients also need to have dementia-related agitation or psychosis that resulted in the prescription of quetiapine from neurology or psychiatry outpatient departments. There must be no other antipsychotic agents either immediately preceding or concurrent with the use of quetiapine. The candidate patients were excluded if they had diagnoses of dementias other than AD or VaD, delirium or other primary psychiatric disorders that warranted the use of antipsychotic agents. They were also excluded if agitation or psychosis were contributed to by other conditions such as significant medical diseases.

**Material and Methods**

Data were collected via medical chart
review. Reviewers were composed of four senior psychiatric residents who were knowledgeable in the diagnosis and management of dementia. A specialist in geriatric psychiatry supervised the work. Demographic data were collected. The reviewers, instead of conducting diagnosis of specific dementia subtypes, relied on the original diagnosis documented by the patients’ neurologists or psychiatrists. Symptoms leading to prescription of antipsychotics, severity of symptoms, improvements on antipsychotic treatment, initial dose and “optimal dose” of quetiapine, time to achieve optimal dose, and concurrent medications were recorded as well.

Definitions of symptom severity, “stable state,” “optimal dose,” and “time to achieve optimal dose.”

Severity of agitation or psychosis was judged through documentations in the charts. “Mild” was designated if symptoms could be calmed down by caregivers without much effort. “Severe” indicated conditions with significant suicidal or violence risks, or conditions calling for hospitalization. “Moderate” severity fell between the mild and the severe. If necessary information couldn’t be drawn, “unknown” severity was given. The definitions of severity were straightforward and akin to daily clinical judgment, the 4 chart reviewers of similar training background achieved high inter-rater reliability (kappa=0.85) on 5 case charts after discussion.

“Stable state” was defined as a period of time lasting for at least four weeks during which (1). there had been at least two clinical visits at an interval of more than four weeks; (2). a constant dose of quetiapine had been maintained throughout; and (3). clinical improvements were achieved and documented in medical charts. If there were multiple stable states, the first one was chosen. “Optimal dose” of quetiapine was defined as the constant dose of quetiapine during the first stable state. “Time to achieve optimal dose” was defined as the time elapsed between the initial prescription of quetiapine and achievement of the optimal dose. Achievement of stable state was assumed to be meaningful clinical effectiveness reflecting both clinical efficacy and acceptable tolerance.

Statistical analysis

Only data from eligible patients achieving stable state were subjected to analysis in this study. Differences of demographic data, clinical correlates and optimal dose between the AD group and the VaD group were examined with student’s t-test for continuous variables and Pearson’s chi-square test for categorical
ones. Within each group, optimal dose was further calculated and compared according to stratification by age (≤ 75 vs. >75), gender and symptoms profiles (agitation alone, psychosis alone, or agitation and psychosis) by student’s t-test or one-way ANOVA. When necessary, linear regression analysis was adopted to explore the relationship between optimal dose and clinical correlates after control of possible confounders.

**Results**

118 patients were included in this study. 49 (41.5 %) patients were diagnosed of AD, and the other 69 (58.5 %) of VaD. Demographic data and clinical correlates of these patients are shown in Table 1. There were no significant differences of demographic data and clinical correlates between the AD and VaD groups, except that significantly more AD patients took cholinesterase inhibitors (CEIs) (53.1 %

| Table 1  Demographic Data and Clinical Correlates of Patients with AD or VaD |
|---------------------------------|-------------------|-------------------|-------------------|
| Characteristics                  | AD Group (n = 49) | VaD Group (n = 69) | Total (n = 118) |
| Age – year                       | 78.2 ± 7.6        | 77.5 ± 7.1         | 77.8 ± 7.3       | 0.614 |
| Female – no. (%)                 | 32 (65.3)         | 43 (62.3)          | 75 (63.6)        | 0.740 |
| Education – no. (%)              |                  |                   |                  | 0.093 |
| Unknown                          | 1 (2.0)           | 7 (10.1)           | 8 (6.8)          |
| Illiterate                       | 6 (12.2)          | 16 (23.2)          | 22 (18.6)        |
| ≤ 9 years of education           | 30 (61.2)         | 30 (43.5)          | 60 (50.8)        |
| > 9 years of education           | 12 (24.5)         | 16 (23.2)          | 28 (23.7)        |
| Symptoms – no. (%)               | 0.363             |                   |                  |
| Agitation alone                  | 10 (20.4)         | 22 (31.9)          | 32 (27.1)        |
| Psychosis alone                  | 23 (46.9)         | 26 (37.7)          | 49 (41.5)        |
| Agitation and psychosis          | 16 (32.7)         | 21 (30.4)          | 37 (31.4)        |
| Source – no. (%)                 | 0.617             |                   |                  |
| Neurology clinics                | 41 (83.7)         | 60 (87.0)          | 101 (85.6)       |
| Psychiatry clinics               | 8 (13.6)          | 9 (13.0)           | 17 (14.4)        |
| Severity – no. (%)               | 0.609             |                   |                  |
| Unknown                          | 11 (22.4)         | 15 (21.7)          | 26 (22.0)        |
| Mild                             | 25 (51.0)         | 29 (42.0)          | 54 (45.8)        |
| Moderate                         | 12 (24.5)         | 21 (30.4)          | 33 (28.0)        |
| Severe                           | 1 (2.0)           | 4 (5.8)            | 5 (4.2)          |
| Concurrent Medications – no. (%) |                   |                   |                  |
| Valproate                        | 2 (4.1)           | 5 (7.2)            | 7 (5.9)          | 0.473 |
| Antidepressants                  | 8 (16.3)          | 19 (27.5)          | 27 (22.9)        | 0.153 |
| Benzodiazepines                  | 3 (6.1)           | 6 (8.7)            | 9 (7.6)          | 0.818 |
| Cholinesterase inhibitors        | 26 (53.1)         | 5 (7.2)            | 31 (26.3)        | < 0.001 |
| Memantine                        | 6 (12.2)          | 0 (0.0)            | 6 (5.1)          | 0.003 |

**Note:** AD: Alzheimer’s disease; VaD: vascular dementia.
Plus-minus values are mean ± standard deviation.
No. (%) denotes number of patients with percentage in the parentheses.
Antidepressants include sertraline, paroxetine, fluoxetine, venlafaxine, trazodone, mirtazapine, and bupropion.
Cholinesterase inhibitors include donepezil, rivastigmine and galantamine.
Table 2  Quetiapine Doses and Time to Optimal Dose of Patients with AD or VaD

<table>
<thead>
<tr>
<th></th>
<th>AD Group (n = 49)</th>
<th>VaD Group (n = 69)</th>
<th>Total (n = 118)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose (mg)</td>
<td>29.9 ± 21.3</td>
<td>33.5 ± 36.2</td>
<td>32.0 ± 30.8</td>
<td>0.526</td>
</tr>
<tr>
<td>Optimal dose (mg)</td>
<td>38.5 ± 37.8</td>
<td>45.7 ± 69.9</td>
<td>42.7 ± 58.6</td>
<td>0.512</td>
</tr>
<tr>
<td>Time to optimal dose (day)</td>
<td>18.2 ± 41.9</td>
<td>17.0 ± 35.2</td>
<td>19.1 ± 46.4</td>
<td>0.786</td>
</tr>
</tbody>
</table>

Note: AD: Alzheimmer’s disease; VaD: vascular dementia. Plus-minus values are mean ± standard deviation.

vs. 7.2%) and memantine (12.1% vs. 0%).

Table 2 presents initial and optimal doses of quetiapine, and time to achieve optimal dose among AD and VaD patients. There were no significant differences found between the two groups. Sub-analysis by gender, age and symptoms (agitation alone, psychosis alone, or agitation and psychosis) in each group showed no significant difference as well. Regarding clinical severity, 26 patients were rated as “unknown”, and only one in the AD group and four in the VaD group were rated “severe.” When the optimal doses of patients with “mild” or “moderate” severity in the AD group were compared with their respective counterparts in the VaD group, there were no significant differences (p values>0.5). Therefore we combined the two groups and examine the dose-severity relationship by linear regression analysis (with optimal dose as the dependent variable). The result suggested a significant association between the optimal dose and clinical severity (p=0.001) (Figure 1). Since concomitant CEI or memantine prescription might represent a confounder, it was then controlled together with age and gender in the regression analysis; the result, however, still indicated a highly significant association between the optimal dose and
clinical severity ($p=0.001$). In contrast, concomitant CEI or memantine prescription itself was not significantly associated with optimal dose of quetiapine ($p=0.390$).

**Discussion**

It was notable that in AD patients the mean optimal dose of quetiapine was 38.5 mg daily, lower than those of previous studies. For example, a 10-week, randomized, double-blind, fixed-dose, placebo-controlled study for nursing home elderly patients with dementia and agitation showed a significant effect in the treatment group with quetiapine 200 mg daily [15]. In another 10-week, double-blind, placebo-controlled, randomized trial of flexibly dosed quetiapine and haloperidol, the mean daily dose of quetiapine read 96.9 mg, although no difference in efficacy was found between the two active treatment groups [18]. In other randomized, placebo-controlled studies or open-label studies, the mean daily dose of quetiapine fell in the range of 77.4 mg to 120 mg for dementia patients with agitation or psychosis [16, 17, 20, 21].

In the CATIE-AD study which recruited 421 outpatients with AD and psychosis, agitation, or aggression, there were no significant differences in effectiveness measured by time to discontinuation for any reason across risperidone, quetiapine, olanzapine, and placebo groups [22]. The daily quetiapine dose in this study was 57.0 mg, also lower than those of other studies. Our study was similar to CATIE-AD in two ways. First, the recruited samples were outpatients rather than inpatients or institutionalized patients, i.e. our studied samples were of a relatively milder severity. Second, the titration of antipsychotics was based on primary care physicians’ clinical judgments, that is, consideration based on both efficacy and tolerability, rather than severity measured by rating scales. These could account for lower mean daily dose of quetiapine in CATIE-AD and our study. Furthermore, most of our patients (85.6%) were from the neurology clinics. Since dementia patients with greater behavioral problems are usually treated in psychiatry clinics, our samples may represent a group of patient with milder severity. This was also supported by the fact that there were many more patients with mild and moderate severity than those with graver severity. It is also possible that psychiatrists are more familiar with the use of antipsychotic agents and tend to prescribe more and higher dose than neurologists.

Very few clinical trials have focused on antipsychotic agents for patients with VaD. Our study suggests that, in treating dementia related agitation or/and psychosis, the optimal dose of quetiapine is not
significantly different between AD and VaD patients. Sub-analysis from an open-label naturalistic study assessing the 4-week efficacy and safety of quetiapine for treatment of geriatric psychotic inpatients in Taiwan showed a mean daily dose of quetiapine 211.5 mg in 13 VaD patients and 196.4 mg for 28 AD patients [23]. The sample population was recruited from acute psychiatric ward, and it was very likely that graver severity required larger daily dose. It is noteworthy that the sample population was also Chinese patients. In our study, significantly more AD patients took CEIs or memantine. To compare the optimal dose between AD and VaD patients, the concomitant use of these two kinds of medications has to be taken into consideration since both have been proved to be capable of improving agitation and psychosis in dementia patients. Our results found that concomitant CEI or memantine prescription was not significantly associated with optimal dose of quetiapine. The findings suggested that optimal dose of quetiapine was greatly influenced by clinical severity but not significantly modified by concomitant prescription of CEIs or memantine.

There were little data regarding antipsychotics treatments for Chinese dementia patients with BPSD. As suggested by previous studies examining schizophrenia patients, the Chinese patients seem to require lower doses of FGA or SGA for psychosis than Caucasian patients [24, 25]. Whether pharmacokinetic and pharmacodynamic factors or diverse clinical practices are accountable for the differences remains uncertain. More well-designed studies are needed to make recommendations for pharmacological treatment in dementia patients from different ethnicities. Though our study showed a lower optimal dose of quetiapine for a group of Chinese patients with dementia, it has to be interpreted cautiously given the facts that it has several limitations. First, it was a retrospective study with data based exclusively on medical records. Certain important information remained unavailable. Medical documents were subject to errors as well. Clinical severity and improvements had to be inferred from the charts. Second, the diagnoses of dementias were adopted from documentation on the medical charts by individual physicians treating the recruited patients. Without a consensus in diagnosis and treatment, the study population was restricted to patients from neurology and psychiatry clinics since neurologists and psychiatrists were believed to be more familiar with the diagnosis and treatment of patients with dementia. Third, definitions of stable state and optimal dose are relatively arbitrary, and different definitions may lead to different results. However,
with the hypothesis that most dementia specialists would follow the expert panel’s advices to discontinue or switch antipsychotics if the treatment doesn’t benefit the patients after 2 to 4 weeks [6], we think that the constant dose in our defined stable state could represent the optimal dose in natural clinical practice settings.

Taken together, our findings suggest a lower optimal daily dose of quetiapine for outpatients with dementia-related psychosis or agitation. The dose was not significantly different between the patients with AD and those with VaD.

Reference


Quetiapine 治療阿茲海默氏病和血管性失智症相關之躁動或精神病症狀

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摘要

目的：第二代抗精神病藥(含 quetiapine)為治療失智症相關躁動或精神病症狀之首選藥物。然而，至於抗精神病藥有效劑量的研究多以患阿茲海默氏病的高加索人種為主。故我們進行一回溯性研究，藉由病歷回顧找出 quetiapine 治療台灣人阿茲海默氏病和血管性失智症相關之躁動或精神病症狀的適當劑量。

方法：由台灣一家醫學中心的病歷資料庫選出符合特定 ICD-9 失智症診斷碼，而且於 2006 到 2007 年間被神經科或精神科醫師處方抗精神病藥的病人病歷。再由病歷回顧，找出符合以下條件的病歷加以分析：(1) 診斷為阿茲海默氏病或血管性失智症；(2) 因躁動或精神病症狀處方 quetiapine；(3) 到達穩定狀態。「穩定狀態」定義為：當 quetiapine 被維持在固定劑量一段期間，且該期間內有相距至少四週以上的兩次回診。穩定狀態時的劑量定義為「適當劑量」。我們比較阿茲海默氏病組和血管性失智症組之適當劑量的差異，及適當劑量與性別、年齡、症狀種類、症狀嚴重度的相關。

結果：在 118 位病人中，阿茲海默氏病組(49 位病人)和血管性失智症組(69 位病人)的人口學及臨床變項上，除了前組有較多病人使用認知促進劑外，其餘都無差異。兩組的每日適當劑量分別為 38.5 毫克(阿茲海默氏病)及 45.7 毫克(血管性失智症)，亦無統計上差異。適當劑量與症狀嚴重度的顯著相關，但與性別、年齡、症狀種類無關。

結論：合併躁動或精神病症狀的血管性失智症及阿茲海默氏病的華人或台灣人，使用 quetiapine 的適當劑量並無統計上差異，但相較於其它白人或高加索族系的研究，華人或台灣人的每日劑量較低。

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關鍵詞：失智症、阿茲海默氏病、血管性失智症、抗精神病藥、quetiapine

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