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ORIGINAL ARTICLE

Dosage and duration of antipsychotic treatment in demented outpatients with agitation or psychosis

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Background/Purpose: The USA Food and Drug Administration (FDA) issued warnings regarding the use of antipsychotics in patients with dementia in 2003 and 2005. We aimed to study the dose and duration of antipsychotic treatment in dementia, and to examine whether physicians' prescription behaviors changed after the FDA warnings.
Methods: Medical charts of outpatients who had Alzheimer's disease, vascular dementia, or mixed dementia were reviewed. Patients must have achieved a clinically stable state for at least 4 weeks after receiving antipsychotic treatment for agitation or psychosis. Demographics, clinical correlates, and duration of antipsychotic treatment were compared among different antipsychotic groups. Because the quetiapine group had the largest sample size, the optimal dose and duration of quetiapine treatment were compared among three time periods (before 2003, 2003–2005, after 2005).
Results: Stable state was achieved in 215 patients (80 had Alzheimer's disease, 117 vascular dementia, and 18 mixed dementia). Most patients (177) took quetiapine, 25 took risperidone, and 13 took sulpiride. The whole sample had a long total duration of antipsychotic treatment

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(median 525 days, mean 707 days). The median dose and total duration of antipsychotic treatment were 1.0 mg/day and 238 days for risperidone, 100 mg/day and 390 days for sulpiride, and 25 mg/day and 611 days for quetiapine, respectively. The optimal dose and total duration of quetiapine treatment decreased significantly after FDA warning in 2005, although the duration remained long. *Conclusion:* The optimal doses of antipsychotics were not higher than those of western reports, but the total duration of antipsychotic treatment was quite long. Although our study suggests the prescription dosage and duration of antipsychotic treatment decreased significantly after FDA warning in 2005, the duration of treatment was still long. Given the serious safety concerns, more effort should be made to avoid unnecessary and prolonged prescription.

Introduction

The prevalence of dementia increases with age, and it was estimated that 24.3 million people had dementia worldwide in 2005 and the number will double every 20 years, reaching over 80 million by 2040.[1] Dementia is a deteriorating disorder accompanied with various distressing neuropsychiatric symptoms. During the course of Alzheimer's disease (AD), up to 90% of patients develop the behavioral and psychological symptoms of dementia, of which psychosis and agitation present in more than half of all patients.[2–4] Furthermore, dementia-related psychosis and agitation have been reported to be associated with decreased quality of life,[5] more rapid cognitive decline,[6] increased burden on caregivers,[7] early institutionalization,[8] and even higher mortality.[9,10]

Although no pharmacotherapy has been approved by the US Food and Drug Administration (FDA) for patients with dementia-related agitation or psychosis, off-label use of antipsychotic agents is common. Before 2005, antipsychotic agents were recommended as the first-line pharmacotherapy for agitated dementia with delusions and as the high-second line for agitated dementia without delusions.[11] Atypical antipsychotic agents are preferred over typical antipsychotic agents as they have fewer extrapyramidal side effects. Many clinical trials revealed a better efficacy for antipsychotic agents as compared with placebo, but there were also inconsistent results. A meta-analysis of 15 placebo-controlled, double-blind, parallel-group trials involving four atypical antipsychotic agents showed only modest efficacy on rating scales for risperidone and aripiprazole, but not for olanzapine.[12] Another meta-analysis focusing on aggression and psychosis in AD showed significant improvements in aggression with risperidone and olanzapine treatment, but only significant improvements in psychosis with risperidone treatment.[13] Unfortunately, antipsychotic agents were noted to be associated with increased risk for cerebrovascular accidents in elderly demented patients, so the FDA issued a "Dear Healthcare Professional" letter in April 2003.[14] Further, meta-analysis found significantly increased mortality rate with 6- to 12-week atypical antipsychotic treatment in patients with dementia.[15] Therefore, in April 2005, the FDA issued a black box warning that antipsychotics could increase mortality risk in demented patients.[16] Considering both the efficacy and adverse effects, clinicians face a decision dilemma when treating patients with agitation or psychosis. Nonpharmacological interventions may be tried first, and when necessary, the lowest dosage and shortest duration of antipsychotic agent treatment are recommended. However, data about physicians' prescribing behaviors in real life practice are missing in Taiwan. Hence we conducted a study to investigate the dosage and duration of antipsychotic treatment in demented outpatients with agitation or psychosis. Specifically, we wanted to investigate: (1) the dosage and duration of antipsychotic treatment in demented outpatients with agitation or psychosis; and (2) whether the prescription behaviors changed after FDA warnings in 2003 and 2005.

Methods

Patients

This was a retrospective study using the chart review method. Elderly patients who were diagnosed as having dementia at neurology and psychiatric clinics were sampled in an exhaustive way according to predefined criteria in the National Taiwan University Hospital. In the first step, all candidate patients were selected from the hospital database if they had a diagnosis of dementia between January 2006 and December 2007. In the second step, patients' eligibility into this study was evaluated by four senior psychiatric residents knowledgeable in the diagnosis and management of dementia through chart review. To be included, each patient must meet five inclusion criteria: (1) diagnosis of AD, VaD, or mixed dementia by a neurologist or a psychiatrist; (2) a mini-mental status examination score between 10 and 26; (3) being prescribed an antipsychotic agent indicated solely for dementia-related agitation or psychosis at outpatient clinics; (4) not receiving any other antipsychotic agent previously or concurrently; and (5) having achieved a predefined "stable state" (definition below). The diagnosis of AD and VaD was based on DSM-IV-TR.[17] Mixed dementia was defined as cognitive decline sufficient to impair independent functioning in daily life resulting from the coexistence of AD and cerebrovascular pathology, documented either by clinical criteria or by neuroimaging findings.[18] Candidate patients were excluded if they had a diagnosis of a primary psychotic disorder, delirium, other dementias (such as Lewy body dementia) that warranted the use of antipsychotic agents, or other conditions (such as concurrent medical disease, medications, substance abuse) contributing to agitation or psychosis.