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Long-term associations between cholinesterase inhibitors and memantine use and health outcomes among patients with Alzheimer's disease

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Abstract

Objectives: To examine in an observational study (1) relationships between cholinesterase inhibitors (ChEI) and memantine use, and functional and cognitive end points and mortality in patients with Alzheimer's disease (AD); (2) relationships between other patient characteristics and these clinical end points; and (3) whether effects of the predictors change across time.

Methods: The authors conducted a multicenter, natural history study that included three university-based AD centers in the United States. A total of 201 patients diagnosed with probable AD with modified Mini-Mental State Examination (MMSE) scores ≥ 30 at study entry were monitored annually for 6 years. Discrete-time hazard analyses were used to examine relationships between ChEI and memantine use during the previous 6 months reported at each assessment, and time to cognitive (MMSE score ≤ 10) and functional (Blessed Dementia Rating Scale score ≥ 10) end points and mortality. Analyses controlled for clinical characteristics, including baseline cognition, function, and comorbid conditions, and presence of extrapyramidal signs and psychiatric symptoms at each assessment interval. Demographic characteristics included baseline age, sex, education, and living arrangement at each assessment interval.

Results: ChEI use was associated with delayed time in reaching the functional end point and death. Memantine use was associated with delayed time to death. Different patient characteristics were associated with different clinical end points.

Conclusions: Results suggest long-term beneficial effects of ChEI and memantine use on patient outcomes. As for all observational cohort studies, observed relationships should not be interpreted as causal effects.

Keywords: Alzheimer's disease; Cholinesterase inhibitors; Memantine; Outcomes; Longitudinal studies

1. Introduction

Since their introduction, cholinesterase inhibitors (ChEIs) and, later, the N-methyl-D aspartate receptor antagonist (memantine) have been shown in short-term clinical trials and longer term open-label extension studies to stabilize or reduce the rate of decline in measures of cognitive function, activities of daily living, and behavior in some patients with Alzheimer's disease (AD) [1–11]. Most rigorous evidence of whether the effects of ChEIs and memantine are sustained over longer periods of time would come from long-duration, prospective, placebo-controlled trials.

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However, such trials are not only costly to conduct, there also are ethical concerns associated with exposing patients to placebo in trials of long duration because ChEIs and memantine have become the standard of care for patients with AD. In the absence of these trials, observational studies based on practice-based populations may be one of the only ways to evaluate the effects of these medications [12].

Several studies have assessed the effects of ChEIs and/or memantine treatment in real-world clinic settings [13–22]. Results from these studies have been mixed. In one of the first observational studies on the effects of ChEI on patient outcomes, Doody and colleagues [13] found slowed decline in cognitive function after a year in patients treated with ChEIs compared with untreated patients. Comparing patients treated with ChEI or ChEI + memantine combination therapy with an untreated earlier cohort of patients, Atri and associates [17] also reported slower decline in cognition and function in the treated group. Persistent treatment has been shown to be associated with slowed decline in cognition and function, but effects may be lost if treatment is disrupted [3,18]. On the other hand, in another study comparing a cohort of patients treated with ChEIs with an earlier cohort of untreated patients, Lopez and coworkers [14,19] reported no association between ChEI use and time to cognitive and functional decline or to death, but significant delays in nursing home admission.

In an earlier study using a large, multicenter cohort of patients with probable AD who were monitored prospectively up to 6 years from early-disease stages, we reported that patterns of ChEI and memantine use changed substantially over time and were consistent with practice guidelines of initiating ChEIs in mild to moderate AD, and adding memantine in moderate to severe AD [23]. In the current study, we take advantage of the availability of important clinical characteristics (eg, comorbid conditions, psychiatric symptoms) that were not controlled for before, the long follow-up period, and more current data, and further investigated the following questions: Are ChEIs or memantine use associated with length of time to reach cognitive and functional outcomes and death? Are these associations stable over time?

2. Methods

2.1. Sample

Data are drawn from the Predictors 2 cohort, consisting of patients recruited from Columbia University Medical Center, Johns Hopkins School of Medicine, and Massachusetts General Hospital. The study was approved by each local institutional review board. The inclusion/exclusion criteria have been described fully elsewhere [24–26]. Briefly, subjects met Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised, criteria for primary degenerative dementia of the Alzheimer type and National Institute of Neurological Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD. Enrollment required a modified Mini-Mental State Examination score ≥ 30, equivalent to approximately ≥ 16 on the Folstein MMSE [27,28]. Clinical diagnosis of AD has been confirmed in 93% of those with postmortem evaluation [26].

Study recruitment began in 1997, when widespread use of ChEIs began in the United States, and is ongoing. After the baseline assessment, patients were monitored annually. Those who missed a particular visit could respond at a subsequent visit. The cohort used in the current analysis included 201 patients who were monitored for up to 6 years and provided data for 785 visits. Of these 201 patients, 13 had 6 years of follow-up visits, 27 had 5 years of follow-up visits, 37 had 4 years of follow-up visits, 34 had 3 years of follow-up visits, and 41 had 2 years of follow-up visits. One hundred twenty-three patients (61%) did not miss any visits, 15 patients (7%) missed one visit, 19 patients (9%) missed two visits, 22 patients (10%) missed three visits, and the rest of the patients missed four or more visits. Median follow-up for the cohort was 4 years (mean, 3.5 years; SD, 2.0).

2.2. Measures

2.2.1. Clinical end points

We used MMSE scores to assess patients' cognitive status and constructed a dichotomous variable indicating an MMSE score ≤ 10 at each visit. We used Blessed Dementia Rating Scale (BDRS) Parts I and II (Instrumental and Basic Activities of Daily Living) to assess patients' functional status and constructed a dichotomous variable indicating a BDRS score ≥ 10 at each visit. We chose these cutoff points because similar scores have been used as outcomes in many studies. Exploratory analyses of neighboring end points (ie, MMSE score ≤ 8 and BDRS score ≥ 8) did not change estimation results substantively. Patient deaths were most often reported by family members when we attempted to complete follow-up visits. For patients who could not be contacted, information on death was obtained through the National Death Index.

2.2.2. Main independent variables: ChEI and memantine use

All prescription and over-the-counter medication use during the previous 6 months were reported at each visit by the patient and informant on a medication acquisition form. Information reported included name of medication, number of days taking the medication, dosage, and number of pills per day. Because ChEIs have been shown to have similar efficacy despite slightly different pharmacological properties, we combined all ChEIs into one group.

Because of the consistency of medication use reported in this sample, we constructed dichotomous variables indicating ChEI and memantine use during the 6 months prior to each assessment as our main independent variables instead