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Original Research Article

Drug cost optimization of cholinesterase inhibitor therapy in advanced dementia: Results of a prospective study of discontinuation

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Abstract

Purpose: *To investigate the effect of discontinuing treatment with cholinesterase inhibitors (ChEIs) on drug costs in patients with advanced dementia.*
Methods: *Severe dementia patients receiving ChEI treatment for over 12 months (n = 43) aged over 65 years (mean age = 82.6 ± 7.5 years) were recruited from 8 nursing homes located in Alicante, Spain. ChEI treatment was discontinued in 23 patients. Here, we report the results from a cost-minimization analysis to evaluate the drug costs with a follow-up period of three months. The drug costs were prospectively analyzed based on drug acquisition costs.*
Results: *At the end of the follow-up, the mean monthly drug costs were €52.68 ± 22.48 in the discontinuation group and €122.54 ± 44.74 in the continuation group - a significant difference of means of -€69.86 (95 % CI, -91.24 to -48.48; p = 0.000). The monthly drug cost reduction for the ChEI discontinuation group was €1,533.35.*
Conclusion: *ChEI discontinuation appears to be a possible option for minimizing treatment costs in institutionalized patients with advanced dementia.*

Keywords: *Dementia, Cholinesterase inhibitors, ChEI, Medication discontinuation, Drug cost, Nursing homes*

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INTRODUCTION

The role of the cholinergic neurotransmitter system in the development of dementia and its contribution to cognitive decline has been well characterized, allowing the establishment of pharmacologic strategies in treatment [1,2]. To date, non-competitive N-methyl-D-aspartate receptor antagonists and cholinesterase inhibitors (ChEIs) are the only two drug types approved as specific treatments. The different available ChEIs (galantamine, rivastigmine and donepezil) show similar safety and efficacy profiles, and are indicated for mild to moderate phases of dementia. In addition, the Food and Drug Administration has approved a combination of donepezil and memantine to treat Alzheimer's disease (AD) in moderate to severe stages. However, the use of ChEIs in advanced phases or for periods of treatment beyond those

considered in the clinical trials (6 – 12 months) is supported by limited evidence.

Therefore, the clinical practice guidelines recommend, for advanced and severe stages (Mini-Mental State Examination < 10), a comprehensive patient assessment based on overall functional and behavioral factors as well as the caregivers' opinion in order to decide whether or not to continue the treatment with ChEIs [3].

The most recent clinical practice guideline has stablished specific recommendations for ChEI discontinuation but with a low quality of evidence [4]. In addition, there are very few cost-effectiveness studies in the literature that focus on advanced stages of dementia.

In the prospective observational study of ChEI discontinuation in institutionalized patients with advanced dementia, ChEI withdrawal was not related with a clinical decline in cognitive function, functional status or behavioral and psychological symptoms of dementia (BPSD) compared to patients who continued the treatment [5]. This cost-minimization analysis aims to investigate the effect of discontinuing the treatment with ChEIs on drug costs in these patients.

METHODS

This cost-minimization analysis included all the patients of a prospective observational study in which the prescribing physician determined to withdraw or continue the ChEI treatment based on the criteria of the clinical practice guidelines and the multidisciplinary assessment [4], with a follow-up of three months. The protocol of discontinuation was to reduce the dose by halving it weekly and until getting to the formulation of lowest available dose. The subjects included were all the institutionalized patients in 8 nursing homes located in Alicante, Spain, aged over 65 years (mean age = 82.6 ± 7.5 years), with diagnosis of advanced dementia and treated with ChEI for over a year (n = 43). Patients with a comorbid disability or psychiatric disorder that could affect the assessment of functional and/or cognitive status were excluded. After three months there were no differences between the groups in terms of cognitive function according to the Mini-Mental State Examination (p = 0.441), BPSD using the Neuropsychiatric Inventory (p = 0.882), or functional status according to the Barthel Index of activities of daily living (p = 0.080) [5].

Here, we report the results from a cost-minimization analysis to evaluate the drug costs with a follow-up of three months. Drug therapy was obtained from the medical history of each patient. Drug costs were calculated using drug acquisition costs.

The study protocol was approved by the Ethics Committee (approval no. MACH-DEM-2018-01) and carried out in adherence to the laws of Spain, the Helsinki Declaration 2008 [6] and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [7]. Informed consent was obtained.

Data analysis

Qualitative data are expressed as absolute and relative frequencies, while quantitative data are shown in the form of mean ±standard deviation (SD). Normality was determined using the Shapiro–Wilk test. The means of the quantitative variables were compared using Student's *t*-test. If data did not follow a normal distribution, then we used the Mann–Whitney U test. SPSS version 24.0 was used for statistical analysis. Values of $p < 0.05$ were considered significant.

RESULTS

ChEI treatment was discontinued in 53.5% (23/43) of the patients. The complete drug costs per patient before the ChEI discontinuation were €124.41 ± 49.86/month, whose 59% (€73.74 ± 43.01) corresponded to ChEIs costs. The complete drug costs were €10.90 lower in the discontinuation group, with no statistically significant difference between the two groups (95 % CI, -41.86 to 20.08; p = 0.482). At the end of the follow-up of three months, however, the drug costs were €52.68 ± 22.48 in the discontinuation group and €122.54 ± 44.74 in the continuation group, a significant difference of means of -€69.86 (95 % CI, -91.24 to -48.48; p = 0.000). The monthly drug costs reduction for all the ChEI discontinuation group were €1,533.35.

We also analyzed the expenditure on drugs to treat the BPSD: €26.42 ± 11.78/patient/month. There were no significant differences between the groups before the ChEI discontinuation (€25.82 ± 10.97 in the ChEI discontinuation group compared with €27.12 ± 12.91; difference of averages of -€1.30 [95% CI, -8.65 to 6.05; p = 0.538]), or at the end of the follow-up (€26.42 ± 10.92 in the discontinuation group compared with €29.65 ± 15.78 in the continuation group; difference of averages of -€3.22 [95% CI, -11.50 to 5.05; p = 0.140]).

DISCUSSION

The drug costs observed in this study before the ChEI discontinuation was €1,492/patient/year, which represents 3.6 % of the €41,669 annual healthcare cost in Spain for a patient with advanced dementia [8-10]. It is far less than the €2,726/patient/year spent on Alzheimer's disease drug costs in the United States [10]. This could be because the pharmacotherapy follow-up carried out in the context of the study and the discontinuation of the inappropriate drugs observed in these nursing homes [12].

ChEI discontinuation was associated with a lower drug costs at the end of the follow-up. We could expect this, considering the high percentage of the cost that ChEIs mean. However, a cost-effectiveness analysis in this population is necessary. Knapp et al. studied patients with moderate and severe stage dementia: although there were no differences in cost between the continuation or the withdrawal of donepezil, continuing the drug proved to be a cost-effective measure in terms of cognitive function, activities of daily living and quality of life [13].

Limitations of the study

The likely limitations of this study are: (1) although the groups are formed by subjects with a severe stage of cognitive impairment, they are not exactly equivalent because the physician usually discontinues the treatment in patients with a worse functional and overall status, and therefore it is difficult to differentiate the effects of ChEI discontinuation on drug costs from the differences that the lack of comparability between the groups may have caused; (2) the values of MMSE were close to the lower limit, and this could hinder the detection of significant changes between the groups.

CONCLUSION

The results of this study indicate that ChEI discontinuation appears to be a possible option for minimizing treatment costs in institutionalized patients with advanced dementia.

DECLARATIONS

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This paper is an excerpt from the doctoral thesis Optimization of anticholinesterase treatment in advanced dementia by integrating the pharmacist into the multidisciplinary team, Uiversity of Granada, Granada, Spain.

Conflict of interest

No conflict of interest associated is with this work

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Both authors, have contributed in every stage of the study: conceived and designed the study, collected and analysed the data, and wrote the manuscript. Both authors read and approved the manuscript for publication.

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