Evidence-based Evaluation of Cholinesterase Inhibitors for Mild Cognitive Impairment

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ABSTRACT

The purpose of this article is to critically appraise the evidence concerning the use of cholinesterase inhibitors compared to no treatment to prevent the progression from mild cognitive impairment (MCI) to Alzheimer disease. The objective was addressed through the development of a structured, critically appraised topic (CAT). This evidence-based methodology incorporated a clinical scenario, background information, structured question, literature search strategy, results, critical appraisal, commentary, and clinical bottom line.

Keywords: Alzheimer disease, amnestic, cholinesterase inhibitors, critical appraisal, evidenced-based, meta-analysis, mild cognitive impairment

A common evidence-based practice (EBP) approach to review the evidence on a clinical topic of importance to patient care is the critical appraisal of a topic (CAT).[1-3] A CAT is organized to provide an efficient, structured, concise summary of the evidence that follows the constructs of the EBP process. A CAT differs from the gold standard systematic review of research evidence because it does not have the same rigor. Whether developed for individual use or for dissemination, producing and sharing CATs help to expand nurse practitioners' (NPs') knowledge of the medical literature.

The purpose of this article is to develop an EBP-guided CAT to answer the clinical question posed by the patient in the following case on treatment of mild cognitive impairment (MCI).

In your outpatient practice you see a 77-year-old woman who is concerned about a 1-year history of short-term memory loss. She is able to lead an independent life without evidence of disability. Her medical history is unremarkable, and there is specifically no prior history of closed head injury, diabetes, or cardiovascular risk factors. Her spouse corroborated this information. Her cognitive risks are negative. A recent neurological evaluation disclosed no reversible cause for her symptoms. Neuropsychometric testing confirmed relatively circumscribed impairment of delayed recall with preservation of other cognitive domains, consistent with a diagnosis of MCI, single domain, amnestic type. She is anxious to prevent progression to Alzheimer disease (AD). She asks about starting pharmacological treatment. As her NP, you decide to use an evidence-based methodology to address her clinical question.

BACKGROUND AND SIGNIFICANCE OF THE CLINICAL PROBLEM

MCI represents a syndrome of cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life.[4,5] There are 2 major categories of MCI, amnestic and non-amnestic, that are further subclassified as single and multiple domains. Amnestic MCI single and multiple domains are the most common prodromes of Alzheimer dementia, whereas the nonamnestic forms can be associated with other degenerative diseases, such as dementia with Lewy bodies, frontotemporal lobar degeneration, and vascular cognitive impairment.[5] The estimated prevalence of MCI in population-based studies ranges from 10% to 20% in people older than 65.

Several longitudinal studies have shown that most persons with MCI are at increased risk for developing dementia, with an annual rate of 5% to 10% in community-based populations. In clinical trials involving patients with amnestic MCI, more than 90% of those with progression to dementia had clinical signs of AD.[6]

This pattern of decline over time has sparked interest in using approved AD pharmacological agents, such as cholinesterase inhibitors (ChEIs), as a treatment strategy to preserve cognitive skills and prevent progression to dementia. At present there are no pharmacological treatments approved by the Food and Drug Administration (FDA) for persons with MCI.[6] However, given the known frequent association of MCI and AD, many clinicians entertain a discussion with individual patients to determine if they would like to consider ChEI treatment at the MCI stage.[6,7] The clinical question of interest is: *Does the use of ChEIs in patients with MCI slow the progression to AD?*

The key EBP constructs to answer this clinical question after identifying the need are to formulate a well-built question; search out preappraised evidence, working down from the hierarchy of sources if none are available; examine and critically appraise the evidence; analyze those articles most pertinent to the question; critically appraise selected evidence; and apply the findings based on patient preferences and values.[1,8,9]

STEP 1. DEVELOPING A FOCUSED, EVIDENCE-BASED CLINICAL QUESTION

A well-formulated question defining the population, intervention, comparison, and outcomes (PICO) of interest will drive the literature search, avoid database language confusion, allow filters to be used effectively to streamline the search process, and assist with selection criteria of the articles for later review.[2,9] The PICO construction should include specific population characteristics, a limited number of outcomes or interventions (1 per question), and the most relevant outcome(s) (1 or 2). Abbreviations and jargon should be avoided.[8]

To address the therapeutic clinical question for this CAT, the following PICO was crafted: In adults (over 19) with MCI (**P**opulation), does treatment with ChEIs (**I**ntervention) compared to no pharmacological treatments (**C**omparison) prevent the progression to AD (**O**utcome)?

STEP 2. SEARCHING AND SELECTING THE EVIDENCE

The key elements in the search strategy for the CAT is to select the largest database that will aid the NP in finding preappraised evidence articles (systematic reviews or meta-analyses); if none are found, the NP should work down the hierarchy of evidence to identify the strongest article(s) to answer the PICO.[2] For those unfamiliar with this evidence scheme, a representation of this evidence hierarchy reflecting the domains of the clinical question (therapy/prevention, diagnosis, harm, prognosis) is available on the Centre of Evidence-based Medicine's Web site (http://www.cebm.net/index.aspx?o=1025). Melynk and Fineout-Overholt[9] also offer a table describing the hierarchy of evidence and the hierarchy for databases.

The production of preappraised evidence articles has been one of the success stories of the EBP movement.[2] A premier database to start the search with is PubMed, a free online database of health care research and practice, available from computers or smart-phones.[1] PubMed allows the searcher to enter text using natural language, which the system then converts to the database's controlled language, known as Medical Subject Heading (MeSH).[10] A helpful feature on PubMed for the EBP searcher is the clinical queries tool, which uses advance filters to extract study designs likely to provide best evidence to answer clinical questions for asking therapy/prevention, diagnosis, causation, and prognosis.[10] The tool sorts results under 3 headings: clinical study categories, systematic review, and medical genetics. This saves time by quickly identifying possible Level 1 articles; if they are not found, then individual randomized clinical trials (RCTs) are shown.[1]

Using the formulated PICO to guide the search, the PubMed database was searched using the natural language terms *mild cognitive impairment*, *cholinesterase inhibitors*, *Alzheimer's disease*, and the Boolean operator *and*. The PubMed feature *clinical queries, therapy, broad* was selected. The feature *systematic review* yielded 17 articles; 7 addressed the PICO question, and a review of the abstracts identified 3 meta-analyses for further review (Figure 1).[11-13]

Using the clinical study category in clinical queries yielded 176 articles. After reviewing the titles of the 176 articles using the PICO criteria, 19 articles were identified for further review of their abstracts to identify research articles with the highest level of evidence that met our PICO outcome criteria. From the abstract review, 2 RCT studies were identified and reviewed. The RCT study by Doody and colleagues was not included because the primary outcome was improvement of cognitive symptoms over 48 weeks, which was not the clinical outcome of interest defined in the PICO.[14] The second RCT study by Lu et al was also not included because the trial studied