

Experience Summary: Cognitive Impairment and Alzheimer's Disease

Evidera scientists are among the leaders in the field of Alzheimer's disease (AD) and cognitive impairment with more than 20 years of experience in health economics, outcomes research and market access studies. This work includes supporting pharmaceutical clients, managed care organizations and regulatory agencies, understanding a broad range of health related costs, natural disease course, treatment outcomes, market landscape and market access and health-related quality of life (HRQoL) research and evidence standards for HRQoL claims. Since 2010, we have conducted more than 70 projects in AD and published the results and methods of this work in more than 60 peer reviewed publications.

Evidera has been actively supporting the needs of numerous pharmaceutical companies in understanding the health and economic value of their marketed and/or in development assets. The Evidera

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team has developed one of the most cited health economic models (The Assessment of Health Economics in AD [AHEAD]) in this therapeutic area. AHEAD has been recognized as one of the leading models in dementia, and was selected by the National Institute for Clinical Excellence (NICE) in the United Kingdom (UK) to quantify health economic outcomes for AD treatments at the time. Evidera has also developed a discrete event simulation (DES) for the evaluation of cholinesterase inhibitors (AHEAD II), with analyses for the UK and Germany presented at a number of scientific meetings. Recently, to address

the evolving needs in health economic evaluation of therapies fueled by scientific developments, we have applied more than two decades of modeling experience and expertise to develop the AD ACE Simulator. AD ACE is a patient-level simulation model developed to assess the health economic value of disease modifying and symptomatic products. It captures the pathophysiology and management of AD, with a focus on simulating the effects of disease modification and early intervention on the progression of the disease. The model covers the full spectrum of AD (i.e., prodromal/mild cognitive impairment [MCI] to severe), includes interactions across multiple components of the physiology, captures multiple biomarkers and their connections to disease progression, and allows for flexible specification of costs and utilities.

Evidera also has a long history of outcomes research in AD including instrument development, validation and translation as well as quality of life studies, advisory boards and patient-reported outcomes (PRO) dossiers. Our scientists developed the Patient-Reported Outcomes in Cognitive Impairment (PROCOG) instrument to measure mild to moderate cognitive impairment symptoms and their impact from the perspective of patients with AD and mild cognitive impairment (MCI). PRO assessment enhances the understanding of disease impact in a range of disorders. The PROCOG demonstrated good to excellent psychometric properties among a sample of older adults with MCI and dementia of the Alzheimer's type (DAT) as well as cognitively intact older adult control subjects and provides a method for collecting unique information on the patient experience of cognitive impairment. Subscales permit focused evaluation of domains relevant to the patient's experience of cognitive impairment.

We also developed instruments suitable specifically for evaluation of patients with

AD including one that addressed functional and HRQoL issues, and a screening tool designed for use by general practitioners. Our researchers also assist in selecting instruments to be used in clinical trials for cognitive impairment in countries around the globe.

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The increasing need for assistance from others is a burdensome and costly challenge for patients with AD and their caregivers. To provide insight into this issue we studied the impact on caregivers of AD patients over an extended time period. This study yielded both objective and subjective measures of burden, including burden specifically associated with cognitive impairment in the patient, the time spent by caregivers in assisting AD patients in achieving their daily living activities, and the caregiver's reactions to the patient. We also compared persistency with treatment (i.e., time from treatment start to treatment discontinuation or treatment switching) for AD patients treated with competing drugs based on drug discontinuation rates using a longitudinal, administrative claims database. Behavioral patterns and drug utilization, particularly psychotropic drugs and mood stabilizers, were evaluated among nursing home residents via a cross-sectional analysis comparing attributes between residents taking a specific drug versus those who did not.

Recent examples and selected publications of some of our AD and Cognitive Impairment work include:

Epidemiology

Study examples

- DES to conduct exploratory analyses of biomarkers (i.e., Florbetaben with PET) for early diagnosis of AD among patients with suspected dementia.
- Provided focused information on the treatment, epidemiology, and burden of illness for AD and MCI that was the basis for health economic and health outcomes strategies for a compound under development.
- Proof of concept study to understand the diagnosis and treatment patterns of AD in the European setting, including a feasibility assessment of available data sources and data analytics methodologies.
- Quantitative systematic literature review of salient symptoms of AD.
- Study of diagnosis and resource use patterns in the UK and Spain for patients with dementia and AD.
- Determined the prevalence of dementia within the Veteran's Administration (VA) population.
- Department of Defense database study on treatment patterns and outcomes of patients treated with a specific AD drug.
- Systematic literature review and meta-analysis of biomarkers in AD.
- Literature-based study of incidence and prevalence of AD and MCI.

Selected publications

Cho K, Gagnon DR, Driver JA, **Altincatal A**, Kosik N, Lanes S, Lawler EV. Dementia Coding, Workup, and Treatment in the VA New England Healthcare System. *Int J Alzheimers Dis*. 2014; 2014:821894. [Epub 2014 Feb 19]

Ward A, Tardiff S, Dye C, Arrighi HM. Rate of Conversion from Prodromal Alzheimer's Disease to Alzheimer's Dementia: A Systematic Review of the Literature. *Dement Geriatr Cogn Dis Extra*. 2013 Sep 28; 3(1):320-332.

Ward A, Crean S, **Mercaldi CJ**, et al. Prevalence of Apolipoprotein E4 Genotype and Homozygotes (APOE ε4/ε4) Among Patients Diagnosed with Alzheimer's Disease: A Systematic Review and Meta-analysis. *Neuroepidemiology*. 2012;38(1):1-17.

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Crean S, **Ward A**, **Mercaldi CJ**, et al. Apolipoprotein E ε4 Prevalence in Alzheimer's Disease Patients Varies across Global Populations: A Systematic Literature Review and Meta-Analysis. *Dement Geriatr Cogn Disord*. 2011;31(1):20-30.

Caro J, **Ward A**, **Ishak K**, et al. What is the Expected Rate of Cognitive Decline for Patients with Alzheimer's Disease? *Long-Term Care Interface*. 2003;4(3):29-34.

Health Economics

Study examples

- A pre-dementia microsimulation model to run cost-efficiency analyses.
- Identification and review of available information on aspects of the economic burden of AD, such as productivity, costs to employers of caregivers, and direct medical costs of caregivers.
- Determined the cost of dementia within the VA population.
- Literature review to obtain and estimate costs, identify areas where further research on economic consequences of AD could fill gaps in knowledge, and suggest the appropriate methodological designs to obtain the data.
- Literature review on cross-national treatment patterns for AD patients to support adaptation of resource use and costs from one country setting to another.

Selected publications

Saint-Laurent Thibault C, Stillman IO, Chen S, Getsios D, **Proskorovsky I**, **Hernandez L**, Dixit S. Cost-Utility Analysis of Memantine Extended Release Added to Cholinesterase Inhibitors Compared to Cholinesterase Inhibitors Monotherapy for the Treatment of Moderate-to-Severe Dementia of the Alzheimer's Type in the US. *J Med Econ*. 2015 Jun 18:1-33.

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Hartz S, Getsios D, Tao S, Blume S, Maclaine G. Evaluating the Cost Effectiveness of Donepezil in the Treatment of Alzheimer's Disease in Germany Using Discrete Event Simulation. *BMC Neurol.* 2012;12:2.

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Getsios D, Blume S, **Ishak KJ**, Maclaine GD. Cost Effectiveness of Donepezil in the Treatment of Mild to Moderate Alzheimer's Disease: A UK Evaluation Using Discrete-event Simulation. *Pharmacoeconomics.* 2010;28(5):411-427.

Getsios D, Migliaccio-Walle K, **Caro JJ**. NICE Cost-effectiveness Appraisal of Cholinesterase Inhibitors: Was the Right Question Posed? Were the Best Tools Used? *Pharmacoeconomics.* 2007;25(12):997-1006.

Revicki DA, Siddique J, Frank L, et al. Cost-effectiveness of Evidence-based Pharmacotherapy or Cognitive Behavior Therapy Compared with Community Referral for Major Depression in Predominantly Low-income Minority Women. *Arch Gen Psychiatry.* 2005;62(8):868-875.

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Caro J, Getsios D. The Long-term Effects of Cholinesterase Inhibitors on Clinical Outcomes and Costs of Alzheimer's Disease in Managed Care Organizations. *Dis Manag Health Outcomes.* 2003;11:617-631.

Kleinman L, Schmier J, Rothman M, Frank L, Beck C. Time and Costs of Managing Specific Disruptive Behaviors in Long-term Care Facilities: A Descriptive Study. *Consultant Pharmacist.* 2002;17:497-507.

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O'Brien J, Shomphe L, **Caro J**. Behavioral and Psychological Symptoms in Dementia in Nursing Home Residents: The Economic Implications. *Int Psychogeriatr.* 2000;12(suppl 1):51-57.

Payne K, Wilson C, **Caro J**, O'Brien J. Resource Use by Dementia Patients and Care Givers: An International Survey of Medical and Social Services and Processes of Long-term Care. *Ann Long-term Care.* 1999;7(7):263-276.

Outcomes Research

Study examples

- Developed the Patient-Reported Outcomes in Cognitive Impairment (PROCOG) instrument to measure mild to moderate cognitive impairment symptoms and their impact from the perspective of patients with AD and MCI.
- Assessment of psychometric properties of the Dependence Scale in large RCTs of patients with mild to moderate AD.
- Developed PRO evidence dossier on the Dependence Scale and prepared for and attended an FDA meeting to discuss the dossier and the use of the Dependence Scale as a secondary endpoint.
- Developed PRO evidence dossier for the Neuropsychiatric Inventory (NPI).
- Literature review of instruments on mild AD/MCI and endpoint selection recommendations.
- Developed utility estimates for clinically relevant disease states for MCI and AD that were used as inputs for a cost-effectiveness model.
- Quantitative systematic literature review to evaluate the appropriateness of existing instruments for measuring behavioral symptoms in patients with AD.

Selected publications

Gordon MF, **Lenderking WR**, Duhig A, Chandler J, Lundy JJ, Miller DS, Pault-Louis E, Doody RS, Galasko D, Gauthier S, Frank L; Patient-Reported Outcome Consortium's Cognition Working Group. Development of a Patient-Reported Outcome Instrument to Assess Complex Activities of Daily Living and Interpersonal Functioning in Persons with Mild Cognitive Impairment: The Qualitative Research Phase. *Alzheimers Dement.* 2016 Jan; 12(1):75-84.

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Frank L, **Matza L**, Hanlon J, et al. The Patient Experience of Depression and Remission: Focus Group Results. *J Nerv Ment Disord.* 2007;195(8):647-654.

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Frank L, **Kleinman L**, Ciesla G, Rupnow MF, Brodaty H. The Effect of Risperidone on Nursing Burden Associated with Caring for Patients with Dementia. *J Am Geriatr Soc.* 2004;52(9):1449-1455.

Ward A, **Caro JJ**, Kelley H, Eggleston A, Molloy W. Describing Cognitive Decline of Patients at the Mild or Moderate Stages of Alzheimer's Disease Using the Standardized MMSE. *Int Psychogeriatr.* 2002;14(3):249-258.

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Frank L, **Revicki D**, Grotzinger K. Quality of Life for Poor African-American Women with Depression. International Society of Quality of Life Research: November, 2001; Amsterdam, Netherlands. Abstract published in *Qual Life Res.* 2001;10(3):275.

Rabins P, Kasper J, **Kleinman L**, Black B, Patrick D. Concepts and Methods in the Development of the ADRQL: An Instrument for Assessing Health-related Quality of Life in Persons with Alzheimer's Disease. *J Ment Health Aging.* 1999;5:33-48.

Market Access

Study examples

- Assessment of the pricing and reimbursement potential in the EU of a new product to treat AD.
- Understanding payer perceptions of a treatment for AD and Parkinson's Disease (PD) psychosis providing strategic insights into the price potential and data generation activities to optimize market access.
- Payer strategy study of AD device due diligence.
- Payer landscape assessment in AD.
- Value message workshop and dossier for a product to treat AD.
- Expert panel on AD imaging.
- Conducted in-depth interviews combined with a web-based survey of physicians to provide a more comprehensive picture of prescribing experiences in dementia.