Presenting author: Cindy Van, PharmD

Affiliations: The Peter Lamy Center on Drug Therapy and Aging, University of Maryland School of Pharmacy, Department of Practice, Sciences and Health Outcomes Research

Title: Pharmacovigilance with Anti-amyloid-β therapies: Building the Economic Case for Improved Medication Safety

Background: As the population over 65 years old in the U.S. continues to grow, the total cost of dementia will rise substantially from $321 billion to nearly $1 million by 2050.[1-2] Persons living with dementia (PLwD) have been shown to rely on emergency departments (ED) as a source for care, along with higher rates of hospital admission, ED revisits and subsequent inpatient stays.[2-3] Together, these patterns contribute to rapidly growing healthcare utilization.

Anti-amyloid-β therapies, approved for early-stage Alzheimer's disease (AD), carry serious risks including amyloid-related imaging abnormalities (ARIA).[4] Approximately 2.2 million individuals in the U.S. are eligible for anti-amyloid-β therapies with this number anticipated to be increasing.[5] As anti-amyloid-β therapies increase in utilization for early-stage AD, there is a critical need for scalable pharmacovigilance to reduce harm among individuals with Alzheimer's disease and related dementias (ADRD) to minimize unnecessary cost and healthcare burden.

Approach: Presentation will highlight a large-language model (LLMs) that helps to reduce the clinical burden by identifying adverse events (AE). Of note, LLMs have the potential to enhance pharmacovigilance and transform detection and optimize clinical workflows.[6]

Results:

- **Cohort Characteristics**: This study included 46 patients who received at least one dose of anti-amyloid-β therapy (61% female), with a median age of 76 years (range, 58–85). We retrieved 20,123 clinical documents spanning clinician documentation, radiology reports, and infusion records. For note-level evaluation, 3,567 eligible notes were processed. After discordance adjudication, 76% (35/46) of patients experienced an AE. The most common AEs were headache (39%, 18/46), dizziness (28%, 13/46), nausea (20%, 9/46), and infusion reactions (11%, 5/46); ARIA-E occurred in 17% (8/46) and ARIA-H occurred in 9% (4/46).
- **Patient-Level Performance**: Using the adjudicated label as a reference, expert review identified 31 true positives, 11 true negatives, zero false positives, and four false negatives. This corresponded to sensitivity 88.6% and PPV 100%. The LLM-augmented workflow identified 35 true positives, seven true negatives, four false positives, and zero false negatives. This corresponded to sensitivity 100% and PPV 89.7%. In clinical review, the LLM-augmented workflow captured four clinically meaningful events not recognized during expert review.
- **Note-Level Performance**: Across 3,567 eligible notes, expert review flagged 81 notes as AE-relevant. The LLM flagged 422 notes as AE-relevant. The overlap between workflows included 76 notes flagged by both expert review and the LLM; 5 notes were expert-flagged but not LLM-flagged; and 346 notes were LLM-flagged but not expert-flagged. Phone messages and calls accounted for 44% (153/346) of the notes that were flagged by the LLM but not by the expert. These notes frequently contained brief, patient- or caregiver-reported symptom descriptions using informal language "feeling weak", "feeling like vomiting", "memory and fatigue issues, particularly after recent infusion," and "patient going downhill and unable to do anything for herself." Overall, the LLM identified 94% (76/81) of the expert-flagged AE notes.

Conclusion: The focus of this work is on the medication safety perspective and will infer economic implications on healthcare utilization. Looking holistically at the direct and indirect costs of anti-amyloid-β therapies, it is essential to understand the economic implications on both the patient and healthcare system.

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