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Letter to the Editor

Adverse Drug Reactions Associated With Cholinesterase Inhibitors—Sequence Symmetry Analyses Using Prescription Claims Data

To the Editor:

Clinicians must balance the likelihood of benefit with the risk of adverse drug reactions (ADRs) when deciding to initiate or discontinue cholinesterase inhibitors.[1,2] The most common pharmacovigilance method is spontaneous ADR reporting. There were 43,753 ADR reports related to cholinesterase inhibitors reported to the World Health Organization (WHO) International Drug Monitoring Program database between 1998 and 2013.[3] These included non-specific reports of cardiac, gastrointestinal, nervous system, and psychiatric disorders. Several of these ADRs are well established (eg, nausea, diarrhea),[4] whereas other ADRs are less well established (eg, seizures). Although spontaneous ADR reporting is useful for signal detection, it is also subject to selective and underreporting.[5] This is particularly true when ADRs are nonspecific, not identified during routine practice, or easily misattributed to the dementia process itself.[6] The objective of this study was to analyze national dispensing data from Australia's Pharmaceutical Benefits Scheme (PBS) between March 2005 and May 2016 to substantiate ADR signals for cholinesterase inhibitors reported to the WHO International Drug Monitoring Program.

Methods

Sequence symmetry analyses (SSAs)[7] were conducted using data from a 10% random sample of dispensing data from the PBS between March 2005 and May 2016. These data comprised patient-level records of all reimbursed medications dispensed by Australian pharmacies. SSA is a signal detection technique used in the postmarketing surveillance of prescription medications that compares the sequence of incident dispensing of an index and marker medication.[7] The index medication is considered the exposure, and marker medication is considered the outcome. The marker medication is used as a proxy for an ADR that the index medication is suspected to cause. All medications were categorized using Anatomical Therapeutic Chemical (ATC) codes recommended by the WHO.[8]

Incident dispensing of a cholinesterase inhibitor (index medication) was defined as the first dispensing, excluding the first 2 years of the data. The cholinesterase inhibitors of interest were donepezil (ATC code N06DA02), rivastigmine (N06DA03), and galantamine (N06DA04). In Australia, these medications are reimbursed for management of mild to moderate Alzheimer disease.

Marker medications were selected for eight ADRs reported to the WHO International Drug Monitoring Program for which there were at least 100 spontaneous ADR reports each. Antiemetics (A04A, N05AB04, A03FA03, A03FA01) were used as a marker of nausea. Proton-pump inhibitors, histamine 2 (H2) antagonists and antacids (A02BC, A02BA, A02A) were used as a marker of dyspepsia. Loperamide and oral rehydration sachets (A07DA03, A07DA53, A07CA) were used as a marker of diarrhea. Oxybutynin (G04BD04) was used as a marker of urinary incontinence. Anticonvulsants (N03A) were used as a marker of seizures. Anxiolytics (N05B) were used as a marker of anxiety. Hypnotics and sedatives (N05C) were used as a marker of insomnia. Antidepressants (N06A) were used as a marker of depression. Data were extracted on incident dispensing of each marker medication during a 52-week observation period before and after the incident dispensing of the index cholinesterase inhibitor. Incident dispensing of the marker medication was defined as the first dispensing after a 52-week washout period before the observation period.

We determined whether the sequence of the two incident dispensings was causal (cholinesterase inhibitor first, then marker) or noncausal (marker first, then cholinesterase inhibitor). Cases where the incident dispensing of the cholinesterase inhibitor and marker medication occurred on the same date were excluded. The adjusted sequence ratio (ASR) with 95% confidence intervals (CIs) was calculated as the ratio of the two sequences (ie, causal to noncausal). The ASR was adjusted for the background rate of change in incident dispensing of each marker medication using the method described by Hallas[7] and validated by Pratt et al.[9] All data management and analyses were performed in R. This study was approved by the Monash University Human Research Ethics Committee.

Results

In total, 11,695 people were initiated on a cholinesterase inhibitor between March 2007 and May 2015. There were 1202 people with incident dispensing for nausea, 1079 for dyspepsia, 389 for seizures, 348 for diarrhea, 261 for urinary incontinence, 1698 for depression, 807 for anxiety, and 963 for insomnia within 52 weeks before or after initiation of the index cholinesterase inhibitor. Incident dispensing was significantly higher for diarrhea (ASR, 1.42; 95% CI, 1.14–1.77), anxiety (ASR, 1.16; 95% CI, 1.01–1.34), insomnia (ASR, 1.19; 95% CI, 1.05–1.36), nausea (ASR, 1.18; 95% CI, 1.05–1.32) and seizures (ASR, 1.26; 95% CI, 1.03–1.55) after initiation of cholinesterase inhibitors than before (Figure 1). Conversely, incident dispensing for dyspepsia (ASR, 0.87; 95% CI, 0.77–0.98) and depression (ASR, 0.77; 96% CI, 0.70–0.85) was lower after initiation of cholinesterase inhibitors. The ASR was not significant for urinary incontinence.

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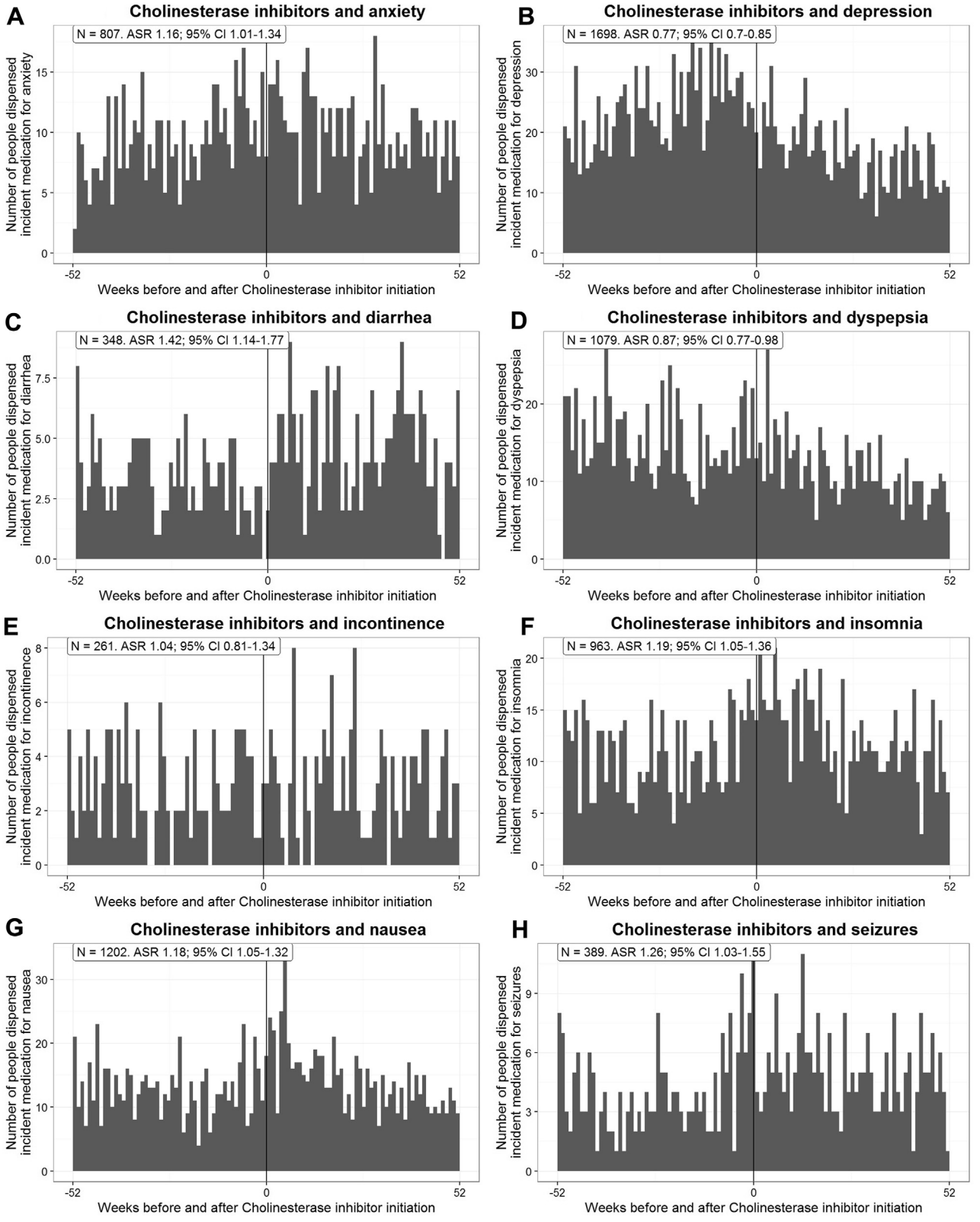

Fig. 1. Sequence symmetry analyses for incident cholinesterase inhibitor and marker medication dispensing (marker for adverse drug reaction). ASR, adjusted sequence ratio; CI, confidence interval.

Discussion

The main finding of this study was an increase in first dispensing of medications for seizures, anxiety, insomnia, nausea, and diarrhea following initiation of cholinesterase inhibitors. There was an inverse association between initiation of cholinesterase inhibitors and initiation of medications for dyspepsia and depression.