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LETTER TO THE EDITOR

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Headache related to use of cholinesterase inhibitors: study of a Cognitive Function Clinic population

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The cholinesterase inhibitors (ChEIs) donepezil, rivastigmine and galantamine are standard treatment for mild-to-moderate Alzheimer's disease (AD). Generally ChEIs are well tolerated [1], with a high retention rate [2]. Common adverse events (nausea, vomiting, diarrhoea, insomnia, muscle cramps) are related to cholinergic stimulation. The British National Formulary also lists headache as a side effect. Pooled donepezil clinical trial data indicated 8%–13% of patients experienced headache as an adverse event (*vs*. 9% in placebo group), which was considered medication-related in about half the patients [3]. To further investigate this, an observational study to measure headache frequency in a Cognitive Function Clinic population prescribed ChEIs was undertaken.

Over a 5.5-year period (January 2001–June 2006 inclusive), 143 patients were commenced on ChEIs (Table 1). In addition to planned follow-up, patients and caregivers were provided with a telephone contact number in case of adverse drug effects.

Two men (aged 70 and 56 years) with mild-to-moderate AD (Mini-Mental State Examination [MMSE] scores 25/30 and 23/30, respectively) complained of new daily headaches with features of tension-type headache within days of commencing donepezil at a low dose (5 mg/day). Headaches were continuous, global in distribution, aching in nature and unrelated to posture. One man noted headache improvement on lying still; he withdrew from treatment, with cessation of headaches and associat-

Table 1 Patient demographics and indications for ChEIs

n	143
M:F	68:75
Age at onset of ChEI treatment	Range: 45–87 years
Duration of ChEI treatment	Range: 1–66 months
Concurrent memantine treatment	7
Indications for ChEI treatment	
AD+mixed AD/cerebrovascular	134
[Early-onset AD	78 (=58%)]
Vascular dementia/vascular cognitive impairment	2
Parkinson's disease dementia/dementia with Lewy bodies	4
Frontotemporal dementia	2
Multiple sclerosis	1

ed nausea. After a drug-free interval of 28 months, he had declined (MMSE 22/30); galantamine was commenced and titrated up to 24 mg/day without headache. In the other patient, simple analgesia controlled headache symptoms but he was unable to increase to donepezil 10 mg/day. Neither patient had a history of prior primary headache disorder or current hypertension.

This pragmatic study suggests that the frequency of ChEI-related headache is very low (1.4%, 95% CI=0.5%–3.3%). Hence, although ChEIs may be responsible for "headache induced by acute substance use or exposure" [4], in clinical practice this is rare, seldom requiring medication withdrawal. Headache mechanism is obscure; it may sometimes be causally related to a cholinomimetic effect [3]. Donepezil has also been reported for migraine prophylaxis [5].

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