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Declining Incidence of Stroke and Dementia: Coincidence or Prevention Opportunity?

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Letters

RESEARCH LETTER

Declining Incidence of Stroke and Dementia: Coincidence or Prevention Opportunity?

Stroke and dementia pose significant threats to the adult brain and share the same treatable risk factors.[1] Stroke incidence in high-income countries has been declining,[2] coinciding with better risk-factor control. However, hitherto there have been encouraging trends, but no proof, of declining dementia incidence.[3] To address this, we analyzed health care administrative data from the Canadian Institute for Health Information for the province of Ontario, Canada.

Methods | We obtained data from the Ontario Health Insurance Plan (OHIP), Ontario Drug Benefit (ODB) Database, Discharge Abstract Database (DAD), and the National Ambulatory Care Reporting System (NACRS). We used intercensal and postcensal projections based on census data from 2001, 2006, and 2011 to estimate the Ontario population. The OHIP physician billing database captures approximately 98% of all physician billings for the province of Ontario and includes diagnosis and procedure codes. The ODB database identifies prescription claims for medications covered under the provincial drug formulary for individuals aged older than 65 years. The DAD and NACRS databases contain diagnosis and procedure information for all hospital admissions and emergency department visits in Ontario. By law in Ontario, all hospital and emergency department admissions are included in these databases, so the sampling frame is population-based.

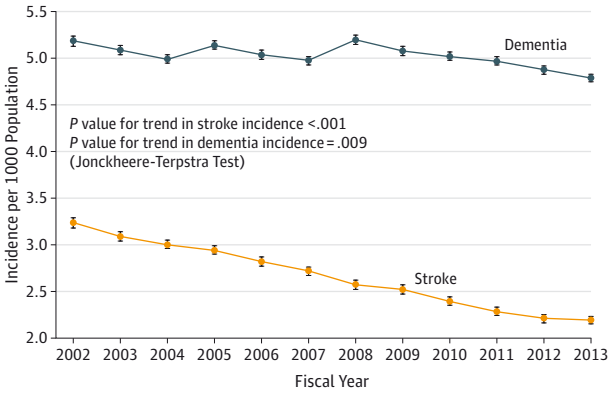
This prospective longitudinal population-based study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board. Patient consent was waived because data collection for the registry is done without patient consent, as the Institute for Clinical Evaluative Sciences is named as a prescribed entity under provincial privacy legislation.

We identified strokes in DAD and NACRS using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes I60, I61, I63, and I64 and OHIP codes 430, 431, 434, and 436. We defined acute stroke as 1 hospitalization (DAD) or 1 emergency department visit (NACRS) with a most responsible diagnosis of stroke, or 2 OHIP claims for physician visits with a diagnosis of stroke within the 365-

Table. Standardized Stroke and Dementia Incidence Rates in Ontario 2002-2013

Fiscal Year	Total Events, No.	Ontario Population (Age ≥20 y)	Standardized Incidence Rate (per 1000 Population)	Standardized Incidence Rate Change, %	Standardized Incidence Rate Change, %
Stroke					
2002	27 496	8 837 824	3.24	−4.63	−32.4
2003	27 036	8 990 356	3.09	−2.91	
2004	27 102	9 139 054	3.00	−2.00	
2005	27 354	9 278 839	2.94	−4.08	
2006	27 031	9 412 650	2.82	−3.55	
2007	26 725	9 526 480	2.72	−5.51	
2008	26 069	9 645 342	2.57	−1.95	
2009	26 242	9 764 722	2.52	−5.16	
2010	25 678	9 907 774	2.39	−4.60	
2011	25 273	10 043 234	2.28	−3.07	
2012	25 357	10 207 127	2.21	−0.90	
2013	25 926	10 351 637	2.19	−4.63	
Dementia					
2002	42 244	8 784 440	5.39	−1.86	−7.4
2003	42 982	8 932 853	5.29	−1.89	
2004	43 817	9 077 583	5.19	+2.89	
2005	46 547	9 212 528	5.34	−1.87	
2006	46 937	9 341 032	5.24	−1.15	
2007	47 724	9 449 484	5.18	+4.25	
2008	51 152	9 559 286	5.40	−2.22	
2009	51 354	9 670 867	5.28	−1.14	
2010	52 308	9 805 265	5.22	−0.96	
2011	53 403	9 932 992	5.17	−1.74	
2012	54 325	10 089 159	5.08	−1.77	
2013	55 340	10 227 315	4.99	−1.86	

Figure. Trends in Stroke and Dementia Incidence Rates, Ontario 2002-2013



The error bars represent 95% CIs.

day calendar year. We used *International Classification of Diseases, Ninth Revision* (290, 294, 331, and 797) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (F00-F03, F05, F06, F09, G30, G31, and R54) codes from DAD, NACRS, and OHIP, as well as ODB claims for cholinesterase inhibitors. We defined dementia as 1 hospitalization (DAD) with any field diagnosis of dementia, 1 physician visit with diagnosis of dementia (OHIP), or 1 prescription for cholinesterase inhibitor (ODB) within the previous year.

We included patients aged 20 years or older, diagnosed as having stroke between April 1, 2002, and March 31, 2014. We excluded patients with invalid health card numbers, missing age/sex, and nonresidents of Ontario. We established a look-back window of 7 years (1995-2001) to exclude cases diagnosed before the study period. As a result, any case identified between April 1, 1995, and March 31, 2002, was not counted, and for each given fiscal year, the individuals with prevalent dementia were also removed from the denominator. Cases with multiple strokes or multiple dementia codes over the study period contributed only once. We calculated stroke and dementia age- and sex-standardized incident rates per 1000 inhabitants for each fiscal year between 2002 and 2013 (12 years).

Results | Between 2002 and 2013, age- and sex-standardized stroke and dementia incidence rates in the Ontario population decreased by 32.4% ($P < .001$) and 7.4% ($P = .009$), respectively (**Table** and **Figure**).

Discussion | To our knowledge, this is the first study showing a decline in dementia incidence over time. This report may also be unique in showing a corresponding decline in stroke incidence in the same population. Previous evidence suggests that diet, exercise, cognitive training, and vascular risk monitoring may improve or maintain cognitive functioning in at-risk elderly people.[4] Hence, primary prevention strategies resulting in improved risk-factor control may have concurrently reduced dementia risk.[5] In addition, given that cerebrovascular disease is an important cause of dementia and that 60 to 80% of all major dementias have a vascular component, the falling incidence of stroke may have further contributed to the decline in dementia incidence.[6]

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Author Contributions: Dr Hachinski had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Sposato, Kapral, Fang, Gill, Hackam, Cipriano.
Drafting of the manuscript: Sposato, Hachinski.
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Study supervision: Hachinski.

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Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies

The skeletal muscle channelopathies include the nondystrophic myotonias and the periodic paralyses. Myotonia is the core clinical feature of the nondystrophic myotonias and may be a feature of hyperkalemic periodic paralysis. It is caused by mutations in the skeletal muscle voltage-gated chloride channel gene *CLCN1* or sodium channel gene *SCN4A*. Adequate treatment of myotonia is important for quality of life, mobility, and functional independence.[1] Mexiletine acts on voltage-gated sodium channels. Its most frequent adverse effect is gastrointestinal[2,3] but minor neurological effects (eg, tremor) are also reported.[4,5] Two randomized clinical trials have demonstrated the efficacy of mexiletine for the short-term treatment of myotonia[2,3] but long-term safety and efficacy data outside a trial setting are lacking. We performed a retrospective review of our large skeletal muscle channelopathy patient cohort to address this.

Methods | All patients with genetically confirmed nondystrophic myotonia or hyperkalemic periodic paralysis prescribed mexiletine with a minimum of 6 months follow-up in our clinic were included. Study data were collected as part of a clinical audit registered with the hospital audit committee. This study received ethical approval from the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics committee. Because data were collected as part of a clinical audit, such evaluations do not require patient consent.

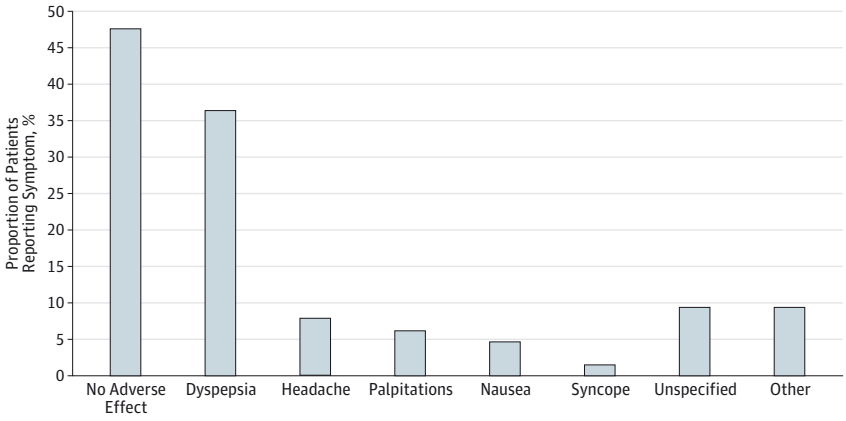
The standard dose titration was increments of 50 to 100 mg of mexiletine per week until symptoms resolved or a total daily dose of 600 mg was reached. Efficacy was determined by patient report. Any symptom or adverse event not clearly attributable to an alternative cause was included. All available electrocardiograms (ECGs) were reexamined. Heart rate, PR interval (P wave to beginning of QRS complex), QRS duration (Q wave to end of S wave), and corrected QT interval (QTc) were noted or calculated manually. The corrected QT interval was calculated using Medcalc (http://www.medcalc.com/qtc.html). Significance was assessed using paired *t* test or 1-way analysis of variance then unpaired *t* test.

Results | A total of 122 patients were identified; 63 met inclusion criteria. Forty patients had mutations in *CLCN1*, 21 in *SCN4A*, and 2 in both *CLCN1* and *SCN4A* (subsequently analyzed with the *SCN4A* group). The mean length of follow-up was 4.8 years (range, 6 months to 17.8 years).

There were no serious adverse events. Paired assessment of ECG parameters while not taking mexiletine and at the highest dose at which an ECG was recorded for each individual revealed no significant change in heart rate (71 beats per minute vs 71 beats per minute; $P = .97$), PR interval (154

Figure 1. Percentage of Patients Reporting Adverse Events While Taking Mexiletine

A Symptoms and adverse events



B Distribution of adverse events

Adverse Event	*SCN4A*	*CLCN1* Missense	*CLCN1* Hom NMD	*CLCN1* Het NMD
Dyspepsia	11	6	4	2
Headache	1	2	2	0
Palpitations	3	0	1	0
Nausea	1	0	2	0
Syncope	0	1	0	0
Unspecified	2	1	3	0
Other[a]	2	2	2	0
None	9	7	5	9

A, Any symptom or adverse event reported while taking mexiletine was included unless there was a clear alternative precipitant. Because some patients reported more than 1 adverse event, the total exceeds 100%. B, Distribution of adverse events by genotype. Because some patients reported more than 1 adverse event, in some cases, the total exceeds the total number of patients in that category. *CLCN1* missense indicates all patients with *CLCN1* missense mutations only (dominant or recessive myotonia congenita); heterozygous (Het) NMD, patients with recessive myotonia congenita with 1 *CLCN1* missense mutation and 1 *CLCN1* mutation associated with nonsense mediated decay; homozygous (Hom) NMD, patients with recessive myotonia congenita with 2 mutations associated with nonsense mediated decay; and *SCN4A* missense, all patients with *SCN4A* mutations.

[a] Other adverse effects were breathlessness (3.1%), vivid dreams (1.5%), tremor and dizziness (1.5%), loose stool, change in ejaculate and fatigue (1.5%), blepharospasm, and the inability to focus (1.5%).