Original Research Article

American Journal of Alzheimer's Disease & Other Dementias®
Volume 37: 1–10

DOI: 10.1177/15333175221124952
journals.sagepub.com/home/aja
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The Association Between Dextromethorphan Use and the Risk of Dementia

Chia-Yuan Chen, MD[1], Chi-Hsiang Chung, PhD[2,3], Wu-Chien Chien, PhD[2,3], and Hsin-Chien Chen, MD, PhD[1]

Abstract

Dementia is one of neurodegenerative disease without preventive medicine currently. Dextromethorphan (DXM) has been reported to reduce neuronal damage and neurodegeneration in animal and human models. The effect of DXM on the dementia has not been fully examined. We examined the medical records over 40 years old in Taiwan's National Health Insurance Research Database between 2000 and 2015 to establish matched cohorts. We used a Cox regression hazard model to identify risk factors of dementia during 16 years of follow-up, and the results indicate that a significantly lower percentage of subjects with DXM use ($P < .001$) developed dementia compared with those without DXM use (11.38%, 4541/39 895 vs 18.66%, 29 785/159 580). After adjustment for age and other variables [adjusted hazard ratio: .567 (95% confidence interval: .413-.678, $P < .001$)], this study also demonstrated that DXM use appeared to reduce the risk of developing dementia. DXM use may potentially provide a protective effect against dementia.

Keywords

dextromethorphan, dementia, Alzheimer disease, cognition decline

Introduction

Dementia is a chronic, progressive neurodegenerative disease characterized by a decrease of cognitive function. Around 55 million people worldwide suffer from dementia, and there are nearly 10 million new cases every year, with Asia estimated to account for 59% of the cases worldwide in 2050.[1,2] The consequent cost and demand for treatment and care of the cognitive declined patients are posing considerable socio-economic impact.

There are many different forms of dementia, with Alzheimer disease being the most common form and possibly contributing to 60-70% of cases.[2] Other major forms include vascular dementia, dementia with Lewy bodies, and fronto-temporal dementia listed in the order of prevalence.[2] Without drugs to cure or reverse the progression of dementia, prevention is still an important strategy in reducing numbers of individuals affected. Elderlies are correlated with multiple drugs use, therefore it is crucial to survey the relationship between these commonly prescribed drugs and dementia.

Dextromethorphan (DXM) has been used extensively and safely as a nonprescription antitussive for about 50 years and is commonly prescribed for treating chronic cough in older population.[3] It is a weak, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, a sigma-1 receptor agonist, a serotonin and norepinephrine reuptake inhibitor, and an α3β4 neuronal nicotinic receptor antagonist.[4,5]

Over the past years, accumulating evidence suggests that DXM has a neuroprotective effect in many central nerve

[1]Department of Otolaryngology-Head and Neck Surgery, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan
[2]School of Public Health, National Defense Medical Center, Taipei, Taiwan
[3]Department of Medical Research, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan

Corresponding Authors:
Wu-Chien Chien, PhD, Department of Medical Research, National Defense Medical Center, Tri-Service General Hospital, 7115R, No. 325, Section 2, Cheng-Kung Road, Taipei 11490, Taiwan.
Email: chienwu@ndmctsgh.edu.tw

Hsin-Chien Chen, MD, PhD, Department of Otolaryngology- Head and Neck Surgery, National Defense Medical Center, Tri-service General Hospital, No. 325, Sec. 2, Rd. Cheng-Kung, Taipei 11490, Taiwan.
Email: acolufreia@yahoo.com.tw

system (CNS) injuries including epilepsy, cerebral ischemia, traumatic brain injury (TBI), and neurodegenerative diseases.[3,6,7] Memantine, which is also a NMDA receptor antagonist, has been approved to treat moderate to severe Alzheimer's disease.[8] Dextromethorphan and quinidine, has also been approved to treat pseudobulbar affect (PBA) in the United States and European Union.[9,10]

To our knowledge, there are no previous or prospective research that focuses on the relation between DXM and its effect on dementia. We conducted a study investigating DXM and its possible association with dementia by utilizing Taiwan's National Health Insurance Research Database (NHIRD) to detect the development of dementia in a Taiwanese population with and without DXM use over a 16-year follow-up.

Materials and Methods

Data Sources and Ethical Consideration

Our data was extracted from the NHIRD of medical claims that were registered from 2000 to 2015. The National Health Insurance (NHI) is a compulsory social insurance health program for all citizens of Taiwan, starting from birth and lasts an entire lifetime. The dataset comprises patient medical information, including demographics, outpatient diagnoses, admission dates, discharge diagnoses, and prescriptions and it covers nearly the entire population. The Institutional Review Board of Tri-Service General Hospital approved this study (TSGHIRB No. 2-106-05-029). Since this is a deidentified database, the IRB waived the requirement of informed consent for this study.

Study Design and Participants Selection

We gathered data from 2000 to 2015, with the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) as the diagnosis system used by the NHI.

We divided the participants into two groups, with DXM use as our study cohort and without DXM use as our reference cohort. The reference group was matched to our control group with 4-fold propensity score by age and index date.

Outcome Measures

All the study participants were followed from the index date until the onset of dementia (ICD-9-CM codes: 290.xx, 294.1 and 331.0~331.2). The date of prescription was set as our index date, and the diagnosis of dementia was set as our primary endpoint. The death of patients, disenrollment from the NHI and the end of the study date (December 31, 2015) were also set as endpoints. For both groups, we excluded patients with use of DXM before index date, dementia before tracking, without tracking, age <40 years and gender unknown. Data from 1998-1999 were first examined and set as a washout period to determine if the dementia was new and if the patient received DXM before index date. We did not obtain data before 1998 so we assumed that if the patient did not have a diagnosis of dementia between year 1998-2000, it is considered a new diagnosis. The same applies for DXM use. If the person had records of DXM prescription during 1998-2000, he will be excluded from the cohort. We also excluded the participants with age <40 years. After the exclusion, we identified a total of 39 895 participants in DXM group and 159 580 participants in non-DXM group. We received 4541 and 29 785 records of dementia, in DXM and non-DXM groups, respectively.

Dose and Duration of Dextromethorphan

The dosage of DXM was calculated by Defined Daily Dose (DDD), an assumed average maintenance dose per day for a drug used for its main indication in adults.[11] The DDD is 90 mg for dextromethorphan. The duration of the usage of DXM was calculated by dividing the cumulative doses by the DDD of DXM. We categorized DXM into three groups (low dose 1-30 DDD, intermediate 31-90 DDD, and high dose ≥91 DDD per year), to survey the potential effects on the risk of dementia.

Statistical Analysis

All data analyses were performed using IBM SPSS for Windows, version 22.0 (IBM Corp, Armonk, NY, USA). The Chi-square test and Fisher's exact test were used to compare the difference of categorical variables, and Student's t test was used to compare the difference of continuous variables between with DXM use and without DXM use. Multivariate Cox proportional hazards regression was used to determine the risk of dementia, and the results are presented as a hazard ratio (HR) with 95% confidence interval (CI). The difference in risk of dementia for patients with or without DXM use was estimated using the Kaplan–Meier method with a log-rank test. The cumulative effects of prescribing DXM were calculated according to DDD, using Cox regression. A 2-tailed P value <.05 was considered statistically significant.

Results

Characteristics of Participants

The study population consisted of 199 475 participants, including 39 895 individuals with DXM use and 159 580 individuals without DXM use (Figure 1). The mean follow-up time was 9.96 ± 9.35 years in the cohort and 9.88 ± 9.26 years in the control cohort. At the time of baseline, the two groups of participants present similarities in age and gender distribution. By the time of endpoint, 4541 in DXM group (11.38%) and 29 785 in non-DXM group (18.66%) was diagnosed with

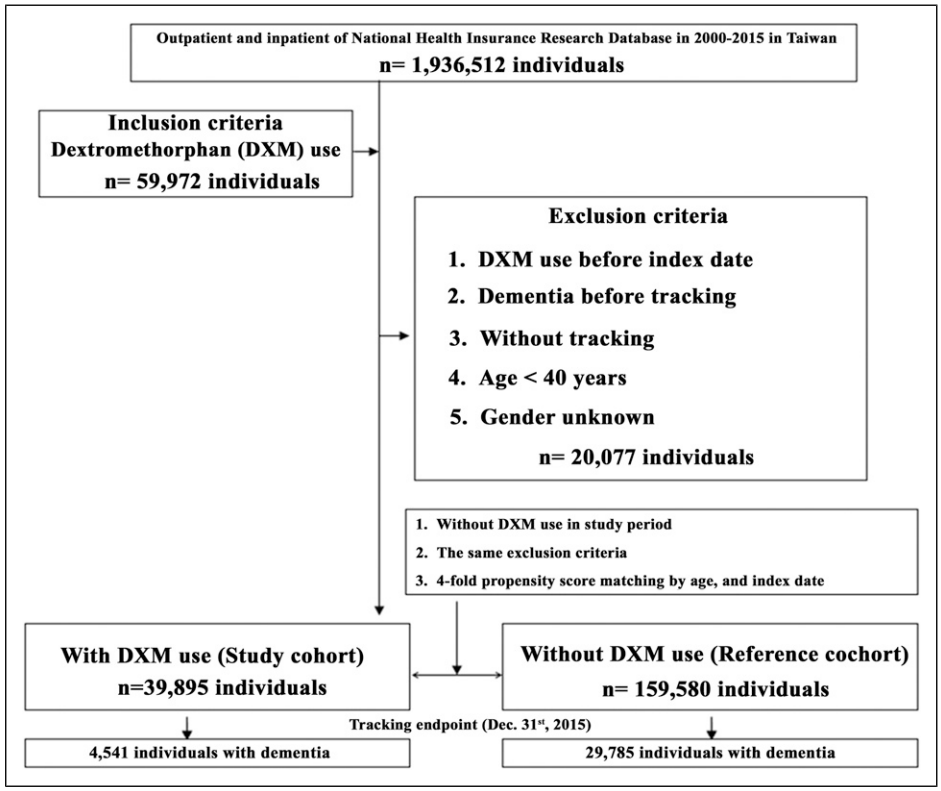

Figure 1. The flowchart of study sample selection.

dementia. The study group showed a lower rate of developing dementia at the end of follow-up than the control group ($P <$ .001) in Table 1.

Factors with higher risk of dementia includes male, higher age, catastrophic illness, diabetes mellitus (DM), hypertension (HTN), depression, stroke, chronic kidney disease (CKD), epilepsy, autoimmune disease (AID), ischemic heart disease (IHD), pneumonia, head injury, alcohol use/dependence, chronic liver disease (CLD), Parkinson's disease, higher urbanization level (Table 2).

Cumulative Risk of Dementia

Overall, the cumulative incidence of dementia showed overall increase as years of follow-up progress. The risk in DXM group is lower compared to non-DXM group with log-rank ($P <$ .001) starting from year one and in every year of follow-up (Figure 2).

Different DXM Dose and Risk of Dementia

To observe then relationship between different dosage and the cumulative risk of dementia, patients were separated into three groups, using Defined Daily Dose (DDD) as criteria. The multivariable-adjusted hazard ratios for dementia compared with non-DXM group, were .75 (95% CI, .54 to .90) for a dose of 1-30 DDD, .56 (95% CI, .40 to .67) for 31-90 DDD, and .44 (95% CI, .32 to .53) for higher than 90 DDD (Table 3). The data indicated that patients using DXM, independent of dosage, exhibited a reduced risk of dementia rates compared with the non-DXM group. Furthermore, there is a dose dependent pattern, where higher dosage of DXM relates with a lower risk of dementia.

Selected Subgroup Analyses

The patients were stratified by the variables presented in Table 1, and adjusted hazard ratio of different subgroups were calculated (Table 4). DXM group encountered 4541 medical events due to first diagnosed dementia in the 489 281 person-years (PY) observed, representing a rate of 928 per 10^5 PYs, while non-DXM patients encountered 29 785 medical events in the 1 845 032 person-years (PY) observed, representing a rate of 1614 per 10^5 PYs. Overall, patients with DXM use shows significant lower multivariable-adjusted hazard ratio .567 (95% CI, .413 to .678) compared to non-DXM group ($P <$ .001).

Every subgroup except patients with catastrophic illness showed significant lower hazard ratio in the DXM group. In both male and female, the hazard risk was similar, .577 (95% CI, .42 to .69) in male and .549 (95% CI, .400 to .657) in female. The hazard ratio in patients with catastrophic illness .861 (95% CI, .627 to 1.029) showed no statistical

Table 1. Characteristics of Study in the Endpoint.

Dextromethorphan	Total		With		Without		
Variables	n	%	n	%	n	%	*P*
Total	199 475		39 895	20.00	159 580	80.00	
Dementia	34 326	17.21	4541	11.38	29 785	18.66	<.001
Gender							.999
Male	100 605	50.43	20 121	50.43	80 484	50.43	
Female	98 870	49.57	19 774	49.57	79 096	49.57	
Age (years)	54.82 ± 25.70		55.28 ± 26.45		54.70 ± 25.51		<.001
Insured premium (NT$)							.094
<18 000	111 348	55.82	22 451	56.28	88 897	55.71	
18 000-34 999	55 417	27.78	11 012	27.60	44 405	27.83	
≥35 000	32 710	16.40	6432	16.12	26 278	16.47	
Catastrophic illness	14 775	7.41	2671	6.70	12 104	7.58	<.001
Diabetes mellitus	19 895	9.97	3884	9.74	16 011	10.03	.076
Hypertension	44 254	22.19	9112	22.84	35 142	22.02	<.001
Depression	5145	2.58	1097	2.75	4048	2.54	.016
Insomnia	8667	4.34	1845	4.62	6822	4.27	.002
Stroke	10 816	5.42	2111	5.29	8705	5.45	.197
Chronic kidney disease	21 379	10.72	4344	10.89	17 035	10.67	.217
Hyperlipidaemia	5683	2.85	1184	2.97	4499	2.82	.111
Epilepsy	1804	.90	429	1.08	1375	.86	<.001
Autoimmune disease	16 646	8.34	3245	8.13	13 401	8.40	.088
Ischemic heart disease	15 279	7.66	2675	6.71	12 604	7.90	<.001
Chronic obstructive pulmonary disease	15 774	7.91	2973	7.45	12 801	8.02	<.001
Pneumonia	26 425	13.25	5671	14.21	20 754	13.01	<.001
Head injury	33 160	16.62	6881	17.25	26 279	16.47	<.001
Asthma	22 200	11.13	4213	10.56	17 987	11.27	<.001
Alcohol abuse/dependence	1656	.83	381	.96	1275	.80	.002
Tobacco abuse/dependence	1539	.77	291	.73	1248	.78	.282
Chronic liver disease	20 165	10.11	4041	10.13	16 124	10.10	<.001
Parkinson's disease	4151	2.08	900	2.26	3251	2.04	.006
Urbanization level							<.001
1 (The highest)	56 147	27.75	12 121	30.38	44 026	27.10	
2	68 507	33.86	13 986	35.06	54 521	33.57	
3	25 893	12.80	5111	12.81	20 782	12.79	
4 (The lowest)	51 778	25.59	8677	21.75	43 101	26.54	
Level of care							<.001
Hospital center	60 690	30.42	14 562	36.50	46 128	28.91	
Regional hospital	80 873	40.54	15 756	39.49	65 117	40.81	
Local hospital	57 912	29.03	9577	24.01	48 335	30.29	

P: Chi-square/Fisher exact test on category variables and t-test on continue variables.

significance when DXM group compared to non-DXM group.

Note that in each subgroup, patients with comorbidities have higher hazard ratio compared to patients without comorbidities. For example, in patients without depression, the hazard ratio is .512 (95% CI, .373 to .612) and in patients with depression, .624 (95% CI, .455 to .746). This pattern can be observed in all subgroups. What is also interesting is that the higher urbanization and the higher level of care correlates with higher hazard ratio, with .778 (95% CI, .566 to .93) in urbanization level 1 (the highest), .384 (95% CI, .28 to .46) in urbanization level 4 (the lowest); and .648 (95% CI, .472 to .775) in hospital center and .516 (95% CI, .376 to .617) in regional hospital.

Discussion

The results revealed that DXM use is related with a significantly decreased risk of developing dementia when compared to non-DXM use, which is consistence with previous evidence that DXM could exert neuroprotective effect in many CNS diseases including epilepsy, cerebral ischemia, TBI and neurodegenerative diseases.[3] The data

Table 2. Factors of Dementia by Using Cox Regression.

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Dextromethorphan	.672	.565	.789	<.001	.567	.413	.678	<.001
Gender (male/female)	1.682	1.029	2.501	.022	1.523	1.007	2.452	.043
Age (yrs)	2.010	1.345	2.394	<.001	1.972	1.226	2.420	<.001
Insured premium (NT$)								
<18 000	Reference				Reference			
18 000-34,999	.903	.598	1.385	.501	.895	.688	1.265	.462
≥35 000	.786	.401	1.211	.568	.723	.562	1.172	.588
Catastrophic illness	2.972	1.865	3.565	<.001	1.863	1.424	2.784	<.001
Diabetes mellitus	2.012	1.269	2.970	<.001	1.952	1.112	2.401	<.001
Hypertension	2.301	1.386	2.984	<.001	1.801	1.436	2.165	<.001
Depression	1.485	1.223	1.706	<.001	1.386	1.065	1.565	<.001
Insomnia	1.298	.449	2.131	.482	1.682	.897	2.765	.304
Stroke	2.597	2.101	3.401	<.001	2.245	1.264	2.872	<.001
Chronic kidney disease	2.561	1.572	3.450	<.001	2.706	1.897	3.801	<.001
Hyperlipidaemia	1.786	1.001	2.301	.049	1.562	.801	1.886	.288
Epilepsy	5.986	3.232	7.889	<.001	1.240	1.016	1.456	.032
Autoimmune disease	2.154	1.642	2.976	<.001	2.295	1.785	2.459	<.001
Ischemic heart disease	1.976	1.333	2.487	<.001	1.865	1.235	1.996	<.001
COPD	1.343	.976	3.010	.073	1.298	.896	2.975	.187
Pneumonia	2.101	1.301	2.899	<.001	2.456	1.597	3.024	<.001
Head injury	10.597	5.124	27.978	<.001	1.862	1.452	2.459	<.001
Asthma	1.004	.349	1.7.2	.483	1.026	.452	1.896	.372
Alcohol abuse/dependence	1.976	1.035	2.701	.026	1.765	1.009	2.652	.040
Tobacco abuse/dependence	1.452	.845	1.986	.114	1.234	.786	1.897	.385
Chronic liver disease	1.565	1.028	1.983	.033	1.798	1.111	2.068	<.001
Parkinson's disease	3.301	1.986	4.865	<.001	2.701	1.852	3.498	<.001
Urbanization level								
1 (The highest)	1.792	1.459	2.506	<.001	1.686	1.452	2.452	<.001
2	1.676	1.235	2.418	<.001	1.587	1.101	2.334	<.001
3	1.489	1.026	2.121	.022	1.331	.956	2.098	.072
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	1.725	1.308	2.140	<.001	2.010	1.452	2.701	<.001
Regional hospital	1.501	1.176	1.997	<.001	1.865	1.226	2.154	<.001
Local hospital	Reference				Reference			

Abbreviations: Adjusted HR, Adjusted hazard ratio: Adjusted variables listed in the table; CI, confidence interval.

indicated that DXM use may provide potential benefits for the management and prevention of dementia.

In Taiwan, several community studies revealed that Alzheimer-type dementia is the most common cause of dementia (40-60% in all dementias), followed by vascular dementia (20-30% in all dementias), and mixed or other dementias (7-15%).[12-14] In our study, 17.21% of our subjects developed dementia at the endpoint; 11.38% in DXM group and 18.66% in non-DXM group, which is higher than the prevalence of 2-3% for the population age among 65-69 years, but lower than the prevalence of >30% for the population age >80 years in community studies.[15] It is possibly because Taiwan has become an aged society with the highest rate of aging compared to the rest of the world and the increased incidence of young onset dementia before the age of 65.[2] Another possibility is our use of ICD-9 code as the diagnosis of dementia, which may lead to including patients with other cognitive impairments and causing overdiagnosis.

The risk factors for dementia includes less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, TBI, and air pollution.[16] Most of the risk factors are similar with our study. Interestingly, hearing loss in the midlife has been associated with an 8% increased risk for dementia.[16] Preventing or treating hearing loss may reduce the consequent risk of dementia. In our previous study, DXM use may have a potential protective effect against sensorineural hearing loss.[17] Thus, this study further supports the additive effect of DXM treatment for dementia related to hearing loss.

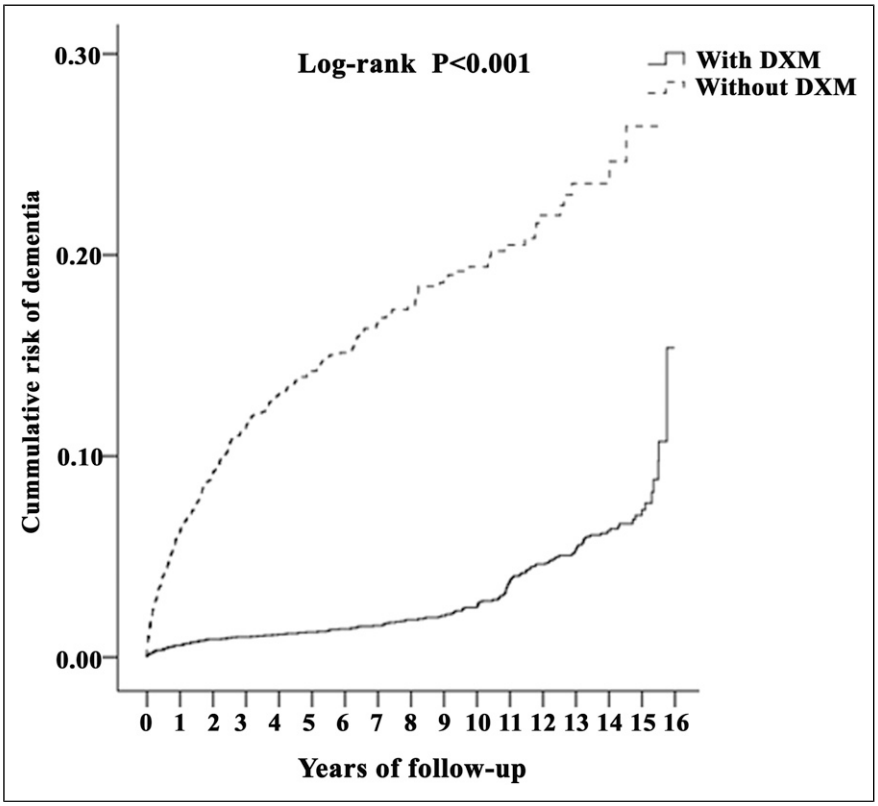

Figure 2. Kaplan-Meier for cumulative risk of dementia among aged 40 and over stratified by dextromethorphan with log-rank test.

Table 3. Factors of Dementia Among Different Dose of Dextromethorphan by Using Cox Regression.

Dextromethorphan Dose	Population	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	*P*
Without	159 580	29 785	1 845 032.15	1614.34	Reference			
With	39 895	4541	489 281.51	928.10	.567	.413	.678	<.001
1-30 DDD	8423	1261	102 435.27	1231.02	.754	.541	.897	<.001
31-90 DDD	19 450	2214	240 978.55	918.75	.563	.404	.673	<.001
≥91 DDD	12 022	1066	145 867.69	730.80	.442	.321	.531	<.001

Abbreviations: PYs, Person-years; Adjusted HR, Adjusted Hazard ratio: Adjusted for the variables listed in Table 2; CI, confidence interval; DDD, defined daily dose.

DXM has been found to be neuroprotective in many preclinical studies and CNS injuries models. One of the mechanisms is its role as a NMDA receptor (NMDAR) antagonist.[3] Excessive glutamate NMDAR activity causes excitotoxicity and promotes cell death, underlying a mechanism in the pathophysiology of neurodegenerative disorders.[18-20] However, past clinical studies are few and yielded poor results.[21,22] One of the suspected reasons is due to significant lower dosage than the required dosage of neuroprotective effect. DXM's neuroprotective effect is only seen at a dosage higher than that used for cough suppression due to its rapid first-pass metabolism in the liver into dextrophan through cytochrome P450 2D6 (CYP2D6) isoenzyme.7 Dextrophan has a similar pharmacological profile to DXM and has been found to have neuroprotective effects in glutamate/NMDA toxicity and ischemia models as well.[3,5,23] However, dextrophan is associated with unwanted phencyclidine-like psychotomimetic side effects.[24,25] To decrease DXM metabolization, quinidine, which is an inhibitor of CYP2D6, was used combinedly to block the drugs first-pass metabolization and increase DXM plasma concentration thus increasing the bioavailability.

Our study demonstrated a decreased prevalence of dementia associated with DXM use without the coadministration of quinidine, which is more promising than past studies. The reason of this may be due to the polymorphism of CYP2D6 enzyme across different ethnic groups. On a population basis,

Table 4. Factors of Dementia Stratified by Variables Listed in the Table by Using Cox Regression.

Dextromethorphan	With			Without			With vs Without *(Reference)*			
Stratified	Events	PYs	Rate (per 10^5 PYs)	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	*P*
Total	4541	489 281.51	928.10	29 785	1 845 032.15	1614.34	.567	.413	.678	<.001
Gender										
Male	2971	246 768.60	1203.96	19 151	930 539.96	2058.05	.577	.420	.690	<.001
Female	1570	242 512.91	647.39	10 634	914 492.18	1162.83	.549	.400	.657	<.001
Insured premium (NT$)										
<18 000	2973	275 344.26	1079.74	20 124	1 027 809.39	1957.95	.544	.396	.650	<.001
18 000-34,999	1323	135 053.72	979.61	8123	513 401.76	1582.19	.611	.445	.730	<.001
≥35 000	245	78 883.54	310.58	1538	303 821.00	506.22	.605	.441	.724	<.001
Catastrophic illness										
Without	1640	456 523.75	359.24	15 583	1 705 088.11	913.91	.388	.282	.464	<.001
With	2901	32 757.76	8855.92	14 202	139 944.04	10 148.34	.861	.627	1.029	.083
Diabetes mellitus										
Without	2530	441 647.24	572.86	16 664	1 659 916.16	1003.91	.563	.410	.673	<.001
With	2011	47 634.27	4221.75	13 121	185 115.99	7087.99	.587	.428	.702	<.001
Hypertension										
Without	2555	377 529.83	676.77	18 539	1 438 727.35	1288.57	.518	.377	.619	<.001
With	1986	111 751.68	1777.15	11 246	406 304.80	2767.87	.633	.461	.757	<.001
Depression										
Without	2696	475 827.65	566.59	19 642	1 798 229.98	1092.30	.512	.373	.612	<.001
With	1845	13 453.86	13 713.53	10 143	46 802.17	21 672.07	.624	.455	.746	<.001
Insomnia										
Without	2591	466 654.00	555.23	20 943	1 766 157.54	1185.79	.462	.336	.552	<.001
With	1950	22 627.51	8617.83	8842	78 874.60	11 210.20	.758	.552	.907	<.001
Stroke										
Without	2515	463 391.72	542.74	16 644	1 744 386.67	954.15	.561	.409	.671	<.001
With	2026	25 889.79	7825.48	13 141	100 645.47	13 056.72	.591	.431	.707	<.001
Chronic kidney disease										
Without	2588	436 005.69	593.57	19 643	1 648 076.87	1191.87	.491	.358	.587	<.001
With	1953	53 275.82	3665.83	10 142	196 955.27	5149.39	.702	.511	.840	<.001
Hyperlipidaemia										
Without	3450	474 760.66	726.68	24 113	1 793 015.61	1344.83	.533	.388	.637	<.001
With	1091	14 520.85	7513.33	5672	52 016.54	10 904.22	.680	.495	.813	<.001
Epilepsy										
Without	1696	484 020.15	350.40	14 743	1 829 134.67	806.01	.429	.312	.513	<.001
With	2845	5261.36	54 073.52	15 042	15 897.48	94 618.79	.564	.411	.674	<.001
Autoimmune disease										
Without	2569	449 484.08	571.54	17 684	1 690 092.46	1046.33	.539	.392	.644	<.001
With	1972	39 797.43	4955.09	12 101	154 939.69	7810.14	.626	.456	.748	<.001
Ischemic heart disease										
Without	2655	456 474.69	581.63	18 681	1 699 307.21	1099.33	.522	.380	.624	<.001
With	1886	32 806.82	5748.80	11 104	145 724.94	7619.84	.744	.542	.890	<.001
COPD										
Without	3545	452 819.95	782.87	23 887	1 697 029.54	1407.58	.549	.400	.656	<.001
With	996	36 461.56	2731.64	5898	148 002.61	3985.06	.676	.492	.808	<.001
Pneumonia										
Without	3231	419 731.05	769.78	23 313	1 605 078.54	1452.45	.523	.381	.625	<.001
With	1310	69 550.46	1883.52	6472	239 953.61	2697.19	.689	.502	.824	<.001
Head injury										
Without	2525	404 891.33	623.62	18 476	1 541 199.59	1198.81	.513	.374	.613	<.001

(continued)

Table 4. (continued)

Dextromethorphan	With			Without			With vs Without *(Reference)*			
Stratified	Events	PYs	Rate (per 10^5 PYs)	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	*P*
With	2016	84 390.18	2388.90	11 309	303 832.56	3722.12	.633	.461	.757	<.001
Asthma										
Without	3088	437 612.30	705.65	22 733	1 637 070.04	1388.64	.501	.365	.599	<.001
With	1453	51 669.21	2812.12	7052	207 962.11	3391.00	.818	.596	.978	.022
Alcohol abuse/dependence										
Without	4155	484 608.84	857.39	27 783	1 830 290.85	1517.96	.557	.406	.666	<.001
With	386	4672.67	8260.80	2002	14 741.30	13 580.90	.600	.437	.717	<.001
Tobacco abuse/dependence										
Without	4224	485 712.62	869.65	27 800	1 830 603.02	1518.63	.565	.411	.675	<.001
With	317	3568.89	8882.31	1985	14 429.13	13 756.90	.637	.464	.761	<.001
Ischemic heart disease										
Without	4091	439 721.75	930.36	27 704	1 658 609.68	1670.31	.549	.400	.657	<.001
With	450	49 559.76	907.99	2081	186 422.47	1116.28	.802	.584	.959	.008
Parkinson's disease										
Without	2940	478 243.70	614.75	21 984	1 807 444.74	1216.30	.498	.363	.596	<.001
With	1601	11 037.81	14 504.69	7801	37 587.41	20 754.29	.689	.502	.824	<.001
Urbanization level										
1 (The highest)	1644	148 654.75	1105.92	7015	500 088.56	1402.75	.778	.566	.930	<.001
2	1510	171 527.54	880.33	8144	619 300.61	1315.03	.660	.481	.789	<.001
3	678	62 682.49	1081.64	6255	236 061.43	2649.73	.403	.293	.481	<.001
4 (The lowest)	709	106 416.74	666.25	8371	489 581.55	1709.83	.384	.280	.460	<.001
Level of care										
Hospital center	1983	178 591.74	1110.35	9012	533 322.74	1689.78	.648	.472	.775	<.001
Regional hospital	1245	193 235.23	644.29	8842	752 869.77	1174.44	.541	.394	.647	<.001
Local hospital	1313	117 454.54	1117.88	11 931	558 839.63	2134.96	.516	.376	.617	<.001

PYs, Person-years; Adjusted HR, Adjusted Hazard ratio: Adjusted for the variables listed in Table 3; CI, confidence interval.

Asians exhibit a marked shift toward overall slower CYP2D6 activity due to the high frequencies (up to 64%, averaging 42%) of the reduced function allele CYP2D6*10.[26] In other populations, the frequencies of CYP2D6*10 range between 3 and 7% and the frequency is the lowest in white Europeans.[27] Due to this, DXM may be much more potent in Asian population.[26,27]

DXM has long been used to treat chronic cough and was recently approved by the FDA for the treatment of PBA in dementia patients with quinidine as a complex drug (Neudexa).[28] Despite being approved for treating PBA, DXM/Quinidine was prescribed by many doctors on dementia patients. A study advocates a more cautious attitude toward off-label use of this drug due to the lack of evidence on its effectiveness on other behavioral symptoms of dementia.[29] Our study may provide evidence that DXM use may decrease the risk of dementia in real world population.

The strength of this study is that it is a national cohort study based on Taiwan's NHIRD, which contains data From Taiwan's compulsory and universal healthcare system. This allowed us to perform the analysis in a real-life setting in an unselected patient population. In addition, patient dropout was avoided and selection bias or recall bias minimized because of the use of routine database records.

The study also has several limitations. First, our study did not include the data of DXM/quinidine use due to unavailability of this drug in the country. Second, the diagnosis of dementia was based on NHIRD dataset using ICD-9 code instead of validated assessment tools (such as Clinical Dementia Rating and Mini-Mental State Examination), thus, data on the severity, scales and stage of dementia, and impact on their caregivers were not available. Third, the subtypes of dementia were not assessed to clarify the association between the risk of different types of dementia and DXM use. Another limitation is NHIRD does not have complete environmental status including smoking habits, dietary habits, exercise habits and others which are all risk factors for dementia.

Conclusion

This population-based cohort study suggested that DXM use may reduce the risk for developing dementia and that cumulative DXM dose showed a more reduced risk for dementia development. Our result required further prospective

randomized clinical trials to clarify the preventive effect against dementia to face the future coming hyper-aged population.

Acknowledgments

We acknowledge the technical support in the form of the National Health Insurance research data provided by the National Health Insurance Administration, the Ministry of Health and Welfare.

Author Contributions

C.-Y. C. initiated the study and wrote the first draft of the manuscript. C.-H. C and W.-C. C. analyzed and interpreted the data. H.-C. C critically revised the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Ministry of Science and Technology, Taiwan (MOST 110-2314-B-016-043 to H.C. Chen), the Medical Affairs Bureau, the Ministry of Defense of Taiwan (MND-MAB-D-111117 to H.C. Chen), the Tri-Service General Hospital Research Foundation (TSGH-A-111003 to H.C. Chen and TSGH-B-111018 to W.C. Chien) and based in part on data from the Health and Welfare Data Science Center, Ministry of Health and Welfare.

Data Availability

The data that support the findings of this study are available from the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of HWDC (https://dep.mohw.gov.tw/DOS/cp-5119-59201-113.html).

ORCID iDs

Chia-Yuan Chen https://orcid.org/0000-0001-8314-9799
Hsin-Chien Chen https://orcid.org/0000-0002-5498-5621

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