

Caregivers' willingness to pay for Alzheimer's disease medications in Taiwan

Mao-Hsuan Huang^{a,b}, Chia-Fen Tsai^a, Wei-Ju Lee^{c,d,e,f,g}, Wen-Fu Wang^{h,i}, Kai-Ming Jhang^h, Shuu-Jiun Wang^{d,g,j}, Jong-Ling Fuh^{d,g,j,*}

^aDepartment of Psychiatry, Division of Geriatric Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^bDepartment of Psychiatry, Taipei Veterans General Hospital, Yuanshan and Suao Branch, Ilan, Taiwan, ROC; ^cNeurological Institute, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; ^dFaculty of Medicine, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan, ROC; ^eDementia and Parkinson's Disease Integrated Center, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; ^fCenter for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; ^gBrain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; ^hDepartment of Neurology, Changhua Christian Hospital, Changhua, Taiwan, ROC; ⁱDepartment of Holistic Wellness, Ming Dao University, Changhua, Taiwan, ROC; ^jDivision of General Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Alzheimer's disease (AD) exerts significant financial expenses on caregivers, and knowledge of caregivers' support for out-of-pocket payment is of great importance for policymaking on the insurance coverage of future AD medication in Taiwan. We aimed to investigate caregivers' willingness to pay (WTP) for a hypothetical curative AD medication and the effect of different factors on the amount of WTP.

Methods: Informal caregivers of patients with AD and informants of patients with amnesic mild cognitive impairment (MCI) were included. An iterative bidding game technique, followed by a dichotomous choice question and a final open-ended question were used to elicit caregivers' maximum WTP. The correlations between the WTP and characteristics of caregiver and patient were analyzed, including sex, educational level, severity of dementia, neuropsychiatric symptoms assessed by Neuropsychiatric Inventory, time needed to support patients assessed by Caregiver Activity Survey, and caregivers' monthly income.

Results: A total of 1134 informal caregivers of patients with AD or MCI were included. Caregivers of patients with AD were willing to pay for a curative AD medication, and their maximum WTP value was higher than informants of MCI patients. Among patients with AD and patients with MCI, caregivers' monthly income was positively correlated with WTP. Apathy subsyndrome was the only factor correlated with percentage of WTP in caregiver's income in the MCI group.

Conclusion: Support for out-of-pocket WTP for a hypothetical curative AD medication was significantly related to caregiver's income.

Keywords: Alzheimer's disease; Caregivers; Cognitive dysfunction

1. INTRODUCTION

Dementia refers to a group of medical conditions characterized by a progressive deterioration in cognitive function beyond what might be expected from normal aging. As dementia progresses, a patient usually becomes dependent on caregivers to provide the basic needs of life.¹ Alzheimer's disease (AD), the most common type of dementia, not only affects the patient but also exerts significant health and financial expenses on their informal caregivers.¹ Informal caregivers are usually close relatives or friends of

the patients, and they are often without payment. These caregivers report high levels of depression, stress, and psychological morbidity.^{2,3} Cholinesterase inhibitors (AChEI) and memantine were approved by the U.S. Food and Drug Administration to treat the cognitive symptoms of AD. These medications are not curative, but they possess efficacy in relieving the symptoms and consequently make patients with AD easier to be taken care of.⁴ Clinical studies, country-specific economic models, and caregiver surveys have shown that caregivers of patients who take AD medications may experience less caregiving time, lower levels of burden, and distress than caregivers of patients who do not take AD medications.⁵⁻⁷ Besides, AD medication treatment has been shown to be a cost-effective strategy for mild-to-moderate AD.⁸ Biogen has listed a phase 3b open-label study for a human monoclonal antibody, Aducanumab; whereas other anti-amyloid therapies have failed phase 3 trials.⁹ The research and development of any new drugs for the treatment of AD requires long-term and large-scale studies, the cost of which is reflected in the drugs' price. Given the high cost of the potential drug candidates, it is important to assess the willingness of potential consumers to pay for them.

Cost-effective analyses (CEAs) and cost-benefit analyses (CBAs) are two tools used to evaluate the economical impact of

*Address correspondence. Dr. Jong-Ling Fuh, Neurological Institute, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: jlfuh@vghtpe.gov.tw (J.-L. Fuh).

Dr. Shun-Jiun Wang, an editor at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 446-452.

Received October 26, 2020; accepted January 18, 2021.

doi: 10.1097/JCMA.0000000000000504.

Copyright © 2021, the Chinese Medical Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

medications on dementia.¹⁰ CEAs compare interventions in non-monetary units by quantifying the cost per unit of health gain that they provide. CEAs cannot determine directly whether the benefits of an intervention exceed its costs, and they do not compare benefits between different outcomes.¹¹ CBAs measure both the costs and the health benefits in monetary units, allowing decision-makers to compare different interventions. Willingness to pay (WTP) is the measure of benefits used in CBAs,¹² and contingent valuation (CV) is a method frequently used to estimate people's WTP.¹³ In CV survey, participants are directly asked to indicate the maximum amount of money they would be willing to pay for a hypothetical reduction in their risk of illness or for an improvement in quality of life, while all the features of a product are held constant except price. Data on WTP would be beneficial to those involved in the marketing of services.¹⁴

Studies applying the CV method to estimate the WTP of informal caregivers for an AD medication have been conducted in Canada and Switzerland.^{15,16} From a small sample of 29 informal caregivers of patients with mild-to-moderate AD in Canada, it was revealed that the caregivers were willing to pay more for an AChEI that can stabilize AD symptoms than the drug's cost.¹⁶ Besides, the study did not find an association between the WTP of caregivers and the behavioral symptoms of the patients. Based on face-to-face interviews with 109 caregivers of AD patients, a survey in Switzerland found that caregivers were willing to pay US\$10 800 per year for a hypothetical curative medication.¹⁵ Caregivers were willing to pay more with increasing wealth, but not with increasing time needed for patient care and supervision. The findings of these studies may be hindered by their small sample size. In addition, the Taiwan National Health Insurance (NHI) program, established in 1995, provides compulsory health insurance to almost all residents of Taiwan (approximately 23 million people). It is a mandatory system with a coverage rate of approximately 99.6% at the end of 2010. In this type of system, the patients and families do not pay the fee of medications or health services directly. Knowledge of caregivers' support for out-of-pocket payment in countries with public healthcare systems is of great importance for policymaking.

The aim of the present study was to examine the willingness of informal caregivers of patients with AD or informants of patients with mild cognitive impairment (MCI) to pay for a new hypothetical curative medication. We also investigated the effect of different factors on the amount of WTP.

2. METHODS

2.1. Participants and data collection

A total of 1201 informal caregivers of patients with AD and informants of patients with amnesic MCI were recruited into this interview-based study between 2012 and 2017. They were identified through their memory clinics of the Taipei Veterans General Hospital, Taichung Veterans General Hospital, and Changhua Christian Hospital in Taiwan. An AD diagnosis was made according to the clinical criteria for probable AD as described by the National Institute on Aging–Alzheimer's Association.¹⁷ A diagnosis of MCI was made according to the revised consensus criteria in 2004.¹⁸ The patients also received a clinical interview, neuropsychological assessments, laboratory tests, physical and neurological examination, and neuroimaging examination (computed tomography or magnetic resonance imaging) to exclude non-AD types of central nervous system pathology. We excluded caregivers who could not communicate in Taiwanese or Chinese. In all, 1134 informal caregivers of patients with AD or MCI were included. The Ethics Committee and Institutional Review Board of all participants' hospitals approved the study. All participated caregivers provided written informed consent.

A structured face-to-face and one-to-one interview was conducted by a trained interviewer at the clinic. The patient was not present during the interview to avoid over pledging and to make caregivers disclose their true WTP value. In the first part of the interview, demographic information was obtained, including age, sex, education of the caregiver and the patient, caregiver's relationship to the patient, whether the caregiver lived with the patient, presence of behavioral and psychological symptoms of the demented patient (delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability aberrant motor behavior, according to the categories of the Neuropsychiatric Inventory [NPI]).¹⁹ NPI Caregiver Distress Scale (NPI-D) was used and it has been proven to be a reliable and valid measure of subjective caregiver distress in relation to neuropsychiatric symptoms measured by the NPI.²⁰ Every caregiver's average monthly household income was collected. It has been recommended that in all CBAs using WTP, the effect of income must be controlled.¹¹ The cognitive status of the patients was evaluated using the Mini-Mental State Examination (MMSE)²¹ and Clinical Dementia Rating (CDR).²² The Caregiver Activity Survey (CAS) was used to measure the time spent by the caregivers in supporting patients with dementia during the previous 24 hours from the time of the test.²³ The time spent on each item was recorded in minutes for six items: communicating with the person, using transportation, eating, dressing, supervising, and looking after one's appearance.²³ We tried to collect this information on weekdays and the items were summed together to yield total hours which were capped at 16 hours/d. The second part of the interview was to obtain caregivers' WTP for a hypothetical medication for AD.

2.2. Willingness-to-pay measures

Four CV methods are common in previous studies to elicit WTP values: open-ended questions, payment cards, bidding games, and dichotomous choice.²⁴ In the open-ended questions, respondents are asked to state their maximum WTP directly.²⁵ Payment cards provide a range of amounts of money for respondents to choose their maximum WTP, which is associated with a range bias.¹⁵ In the bidding game, respondents are asked to accept or reject an offer. Depending on their answers, the bid is increased or decreased until the maximum WTP is reached. The bidding game is associated with a starting point bias.²⁴ In the dichotomous choice methods, respondents are only given one bid which they can accept or reject. However, no maximum WTP is directly obtained by this method and there is a risk of overestimation.²⁶

In our study, an iterative bidding game technique was used to explore WTP, followed by a dichotomous choice question (yes or no to the bid offered) and a final open-ended question to elicit caregivers' maximum WTP. First, the informal caregiver was asked whether he or she was willing to pay an out-of-pocket expense for a hypothetical medication, which could cure AD and result in the elimination of behavioral and psychological symptoms under continuous use. The first bid was randomly allocated from one of the seven bids to the caregivers (new Taiwan dollars, NTD3000, NTD6000, NTD9000, NTD15 000, NTD25 000, NTD35 000, NTD50 000) representing monthly out-of-pocket costs, so as to prevent sequencing effect. Based on their responses, the interviewer doubled the first bid for caregivers answering "Yes" and halved the first bid for respondents answering "No". The question was repeated for two rounds. However, caregivers only gave yes/no responses, which may lead to overestimated WTP values. Therefore, we opted for a final open-ended question to check the internal consistency of the obtained values. A combination form of bidding games and open-ended questions has been used in previous studies and has

provided practical insight on policymaking of public health.²⁷ Caregivers' maximum WTP was the highest amount of value obtained from the two CV methods. For caregivers who rejected all two bids, their maximum WTP was their maximum specified amount from the open-ended question. The percentage of maximum WTP value in caregivers' monthly income was collected, because the wealth share puts a limit imposed by ability to pay, avoiding the stated WTP to inflate. Thus, the WTP value was also expressed as a percentage of monthly income. All monetary values are reported in new Taiwan dollars. Based on the average exchange rate from 2012 to 2019, 1 US dollar was worth an average of 30.59 NTD.

2.3. Statistical analysis

Descriptive statistics are reported either as means with standard deviations or as proportions. Student's *t* tests and chi-square tests were used to compare the continuous and categorical variables, respectively, among patients with AD and MCI. Linear regression was used to analyze the effects of independent variables on the maximum WTP value for a hypothetical curative AD medication. First, the age, sex, education, and total MMSE of the patients; the age, sex, education, and monthly income of the caregivers; and NPI-D and CAS reported by the caregivers were used as independent variables in univariate analyses to identify any potential predictive variables. Variables with a *p* < 0.2 according to univariate analyses were included in the multivariate linear regression analysis to determine any independent predictors of the outcome variables.²⁸ The consistency of four neuropsychiatric subsyndromes of the NPI—hyperactivity, psychosis, affective symptoms, and apathy—has been determined

across dementia subtypes, age, and gender.²⁹ We applied subsyndromes of NPI instead of individual symptoms, for they can give more insight into possible relationships between neuropsychiatric symptoms and risk factors of dementia and serves as potential variables. A stepwise (backward) selection method was used. The diagnosis of multicollinearity (variance inflation factor) was conducted in regression analyses and showed no collinearity. Subanalyses stratified by the relationship between caregivers and the patients, or dementia severity by CDR were examined to explore the influence of relationship with patients and dementia severity on caregivers' WTP value. For all variables, significance was defined as two-tailed *p* value < 0.05. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc., Chicago, IL, USA).

3. RESULTS

In this study, 1134 informal caregivers of patients with AD or MCI stated their WTP for a hypothetical medication of AD. Demographic and clinical statistics of the patients and their informal caregivers are presented in Table 1. The patients surveyed were equal in sex, but their caregivers were mostly female, with 586 (66.8%) female caregivers of patients with AD and 177 (68.9%) female informants of patients with MCI. Patients with AD were older than patients with MCI with an average age of 78.4. More informants of patients with MCI lived with the patients compared with caregivers of AD patients. Patients with AD had lower scores on MMSE, higher scores on all NPI-D subsyndromes, and more time needed for caring in all six items

Table 1
Demographic data of patients with AD and mild cognitive impairment and their caregivers

n (%) or mean ± SD	Patients with AD (n = 877)	Patients with mild cognitive impairment (n = 257)	<i>p</i>	
Age, y	78.40 ± 7.78	72.38 ± 8.77	0.005	AD > MCI
Male	433 (49.4%)	121 (47.1%)	0.524	
Education, y	9.31 ± 4.70	10.62 ± 4.30	0.126	
Total MMSE	18.25 ± 5.66	26.09 ± 2.58	0.000	MCI > AD
Caregiver				
Age, y	57.08 ± 13.37	57.47 ± 15.45	0.000	MCI > AD
Male	291 (33.2%)	80 (31.1%)	0.760	
Education, y	13.54 ± 4.59	14.05 ± 5.91	0.837	
Lives with patients	525 (59.9%)	181 (70.4%)	0.000	MCI > AD
Monthly income				
<US\$700	268 (29.4%)	89 (34.6%)	0.222	
US\$700-US\$1400	191 (21.8%)	38 (14.8%)	0.013	AD > MCI
US\$1400-US\$2100	171 (19.5%)	50 (19.4%)	1.000	
>US\$2100	247 (28.2%)	80 (31.1%)	0.389	
NPI-D				
Hyperactivity	3.28 ± 4.716	1.02 ± 2.70	0.000	AD > MCI
Psychosis	2.86 ± 4.30	0.45 ± 1.40	0.000	AD > MCI
Affective	1.72 ± 2.39	0.79 ± 1.67	0.000	AD > MCI
Apathy	1.82 ± 2.76	0.43 ± 1.51	0.000	AD > MCI
CAS, min/d				
Communicating	76.23 ± 153.17	19.44 ± 66.54	0.000	AD > MCI
Transportation	40.37 ± 76.48	10.37 ± 35.30	0.000	AD > MCI
Dressing	13.81 ± 31.81	2.19 ± 10.75	0.000	AD > MCI
Eating	34.65 ± 55.71	6.38 ± 24.58	0.000	AD > MCI
Grooming	15.73 ± 37.31	1.92 ± 11.02	0.000	AD > MCI
Supervision	94.98 ± 268.90	8.90 ± 92.44	0.000	AD > MCI
Amount of willingness to pay, NTD	16 321.55 ± 26 016.27	13 126.07 ± 17 012.18	0.018	AD > MCI
% of willing to pay	24.69 ± 25.14	20.30 ± 23.29	0.109	

AD = Alzheimer's disease; CAS = Caregiver Activity Survey; MCI = mild cognitive impairment; MMSE = mini-mental state examination; NPI-D = Neuropsychiatric Inventory Caregiver Distress Scale; NTD = new Taiwan dollars.

on CAS. Caregivers of patients with AD were willing to pay for a curative AD medication, and their maximum WTP value was higher than informants of MCI patients. The monthly income and the percentage of maximum WTP value in caregivers' and informants' monthly income did not differ between the two groups.

Table 2 shows the univariate and multivariate regression models for determinants of supporting out-of-pocket payment. The sex and education of the patients and their caregivers, the caregivers' income, the affective subsyndrome in NPI-D, and eating in CAS were included in the multivariate analysis in the AD group. The age and sex of the caregivers, the caregivers' income, the hyperactivity, and apathy subsyndrome in NPI-D were included in the multivariate analysis in the MCI group. Among the included variables, caregivers' sex was positively associated with the amount of WTP in patients with AD. No correlation between WTP and CAS or subsyndromes on NPI-D was observed among the AD group. In patients with MCI, their caregivers were more willing to pay for a hypothetical treatment if caregivers suffered more distress from patients' apathy symptoms. Among patients with AD and patients with MCI, caregivers' monthly income was positively correlated with WTP. There was a trend of higher WTP when the caregivers had a higher income. Regarding multivariate regression for percentage of income, no variables included in the models displayed significant association in the AD group (Table 3). In the MCI group, apathy subsyndrome was the only variable correlated with percentage of WTP in caregiver's income.

We stratified caregivers according to their relationship with patients into spouse, offspring, siblings, and others. No significant difference was observed on WTP between the four groups and the relationship with patients was not associated with either maximum WTP or percentage of WTP in salary. We performed subanalyses by separating patients with AD into mild, moderate, and severe groups by using CDR. Patients with severe AD had higher scores on NPI-D and CAS compared with patients of mild or moderate AD, but their caregivers' WTP did not differ between groups.

4. DISCUSSION

We found that male and monthly income of caregivers of AD patients were positively associated with caregivers' WTP. Caregiver's monthly income was the only variable correlating to WTP among patients with AD and MCI, suggesting it to be an important determinant of caregiver's out-of-pocket WTP. However, one should note that the stated WTP from respondents is likely to be influenced by their ability to pay. And the ability to pay is directly affected by income. To avoid income effect, our survey included not only the amount of WTP, but also the percentage of income caregivers were willing to pay. Caregivers' gender was no longer a determinant in multivariate regression for percentage of income. Gender differences among dementia caregivers are thought to explain a proportion of the variance in caregiving outcomes.³⁰ However, results from previous studies were mixed and not all consistent.³¹ The impact of gender on caregiving outcomes may be mediated by variables including role expectations, social support, effects of kinship status, culture, and ethnicity. Future WTP studies should incorporate qualitative methodologies to better investigate the relationships between gender, as well as other sociodemographic variables and their collective influence on WTP. The age of the caregivers was not a determinant for WTP in the present study, which was in contrary to a study showing that older caregivers had lower odds of supporting payment for an AD medication.³² This may be because our recruited caregivers (median age was 56 years) were younger than caregivers in the previous study (median age was 69 years).

Behavioral and psychological symptoms of dementia (BPSD) are connected with caregiver burden.³³ Among these symptoms, delusions, agitation, and irritability seem to exert the most impact on caregiver burnout.³⁴ However, we found no significant associations between WTP and subsyndromes on NPI-D in the AD group. We further tested NPI severity scale and each separate symptom, but still found no association with WTP. It seems that although scores on NPI-D were higher on patients with AD than on patients with MCI, they were not determinants of WTP in the AD group. A recent study examining caregiver's WTP for nonpharmacological treatment of dementia in the United States has revealed a similar finding that clinical features of dementia may not predict WTP.³⁵ Instead, the caregivers' status may be more directly related to their WTP.³⁶ There is a need to include more determinants of caregivers' status in future analysis of different regions and cultures, while most studies were performed in western countries. Apathy was the only subsyndrome correlated with maximum WTP and percentage of income among patients with MCI in our study. It is of interest to note that among symptoms of MCI, apathy exerts a great impact on daily functioning, leading to increased reliance on caregivers.³⁷ Our finding provided a clue as to caregivers' concern for symptoms of MCI. Although there is currently no indicated medication for MCI, future studies may try to investigate caregivers' WTP for nonpharmacological interventions targeting at certain symptoms of MCI. As patients with MCI have high risk of conversion to dementia, whether there are changes on a caregiver's burden and attitude toward WTP for different BPSD in the course of dementia warrant studies.

By combining bidding games technique and open-ended question, the WTP values in our study were obtained by both indirect and direct survey. While indirect survey (eg, bidding games) measures revealed preference, direct survey (eg, open-ended questions) involves asking caregivers directly about the amount of money they are willing to pay. The power of indirect approach may be limited if the evaluated intervention had no similar product sold on a market.³⁸ Because there is currently no cure for AD, it would be appropriate to add a direct survey in the study. During the interview, the benefits beyond the curative AD medication were not explicitly presented in the scenario. It may be argued that caregivers may not be able to provide valid and consistent responses to the hypothetical WTP question. Given that only informal caregivers for patients with dementia were included and interviewed in our study, this issue was less likely to have been a major problem.

Knowledge of caregivers' support for out-of-pocket payment conveys important policymaking information. Insurance reimbursement rules for AD medications differ according to disease severity and drug effects. According to the Taiwan NHI reimbursement criteria, mild-to-moderate dementia includes an MMSE score of 10 to 26 or a CDR score of 1 to 2, moderate dementia includes an MMSE score of 10 to 14 or a CDR score of 2, severe dementia includes an MMSE score 5 to 9 or a CDR score 3. The patients should be re-evaluated for treatment response every year, and the treatment should be stopped if MMSE scores decrease by ≥ 2 points or CDR scores by ≥ 1 point compared with the previous year. Memantine is indicated for moderate-to-severe dementia, with an average cost of NTD140 to NTD558 person-month. Rivastigmine is indicated for mild-to-moderate dementia, with an average cost of NTD966 to NTD1932 person-month. Donepezil is indicated for mild-to-severe dementia, with an average cost of NTD1920 person-month. The expense of the drugs was covered by NHI if the patient met the reimbursement criteria. We asked caregivers how much out-of-pocket payment they were willing to pay for the treatment. This approach may not be the conventional way to estimate WTP, as this is not the usual mode of payment for

Table 2
Univariate and multivariable analyses for amount of the maximum willingness-to-pay

	Patients with AD				Patients with MCI			
	Univariate		Multivariable ^a		Univariate		Multivariable ^a	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Age, y	-47.9 (-269.9, 174.0)	0.672			-42.8 (-282.0, 196.5)	0.725		
Sex (male)	-2893.2 (-6338.5, 552.2)	0.100	-430.8 (-3958.7, 3097.0)	0.811	-1364.3 (-5555.8, 2827.3)	0.522		
Education, y	453.8 (87.3, 820.3)	0.015	274.1 (-91.4, 639.6)	0.141	-36.4 (-524.6, 451.9)	0.884		
Total MMSE	174.8 (-131.1, 480.7)	0.262			59.6 (-753.6, 872.8)	0.885		
Caregiver								
Age, y	-35.2 (-164.7, 94.3)	0.594			-175.3 (-314.3, -36.3)	0.014	-50.4 (-188.5, 87.8)	0.473
Sex (male)	5910.8 (2262.7, 9558.8)	0.002	4232.6 (719.6, 7745.5)	0.018	-3087.6 (-7671.4, 1496.1)	0.186	-2613.8 (-7862.4, 634.8)	0.095
Education, y	1060.5 (687.5, 1433.4)	0.000	359.4 (-16.1, 734.8)	0.061	181.9 (-189.4, 553.2)	0.335		
Lives with patients	1886.2 (-1654.0, 5426.3)	0.296			-3854.3 (-8732.9, 1024.4)	0.121	489.1 (-4268.4, 5246.7)	0.840
Monthly income								
<US\$700	-1557.8 (-19 176.4, -11 977.1)	0.000	Reference		-13 558.5 (-17 629.4, -9487.6)	0.000	Reference	
US\$700-US\$1400	-6932.4 (-11 086.9, -2777.9)	0.001	5317.6 (860.0, 9775.3)	0.019	-3714.8 (-9596.0, 2166.3)	0.215	5624.6 (-554.5, 11 803.7)	0.074
US\$1400-US\$2100	47.3 (-4307.2, 4401.9)	0.983	10 059.1 (5402.3, 14 715.9)	0.000	3804.0 (-1464.7, 9072.7)	0.156	12 092.2 (6371.0, 17 813.4)	0.000
>US\$2100	22 138.2 (18 595.1, 25 681.3)	0.000	25 175.1 (20 871.1, 29 479.17)	0.000	13 719.6 (9525.8, 17 913.5)	0.000	18 568.8 (13 461.5, 23 676.1)	0.000
NPI-D								
Hyperactivity	-156.8 (-522.7, 209.1)	0.400			598.8 (-174.3, 1372.0)	0.128	-689.4 (-1808.3, 429.5)	0.226
Psychosis	-202.1 (-603.4, 199.3)	0.323			560.8 (-930.6, 2052.1)	0.460		
Affective	517.5 (-204.6, 1239.6)	0.160			294.5 (-962.4, 1551.5)	0.645		
Apathy	142.3 (-483.0, 767.6)	0.655			1506.5 (126.2, 2886.7)	0.033	1967.9 (2.2, 3933.6)	0.050
CAS, min/d								
Communicating	1.2 (-10.2, 12.5)	0.842			-8.9 (-41.0, 23.2)	0.585		
Transportation	-12.4 (-35.1, 10.2)	0.282			0.6 (-60.0, 61.1)	0.985		
Dressing	-12.4 (-66.9, 42.1)	0.655			72.8 (-126.0, 271.6)	0.471		
Eating	23.8 (-7.3, 54.8)	0.134	27.3 (-1.9, 56.5)	0.067	2.3 (-84.7, 89.3)	0.959		
Grooming	-7.0 (-53.4, 39.4)	0.767			19.9 (-174.1, 213.9)	0.840		
Supervision	-3.0 (-9.4, 3.5)	0.367			-7.1 (-30.2, 16.0)	0.545		

^a Bold type indicates statistical significance.
 AD = Alzheimer's disease; CAS = Caregiver Activity Survey; CI = confidence interval; MCI = mild cognitive impairment; MMSE = mini-mental state examination; NPI-D = Neuropsychiatric Inventory Caregiver Distress Scale.
^b Analyzed by backward elimination for multiple linear regression.

Table 3**Univariate and multivariable analyses for percentage of willingness-to-pay in caregiver's income**

	Patients with AD				Patients with MCI			
	Univariate		Multivariable ^a		Univariate		Multivariable ^a	
	β (95% CI)	<i>p</i>	β (95% CI)	<i>p</i>	β (95% CI)	<i>p</i>	β (95% CI)	<i>p</i>
Age, y	-0.18 (-0.41, 0.05)	0.133	-0.14 (-0.37, 0.10)	0.262	0.12 (-0.23, -0.46)	0.510		
Sex (male)	-3.07 (-6.74, 0.59)	0.100	-2.77 (-6.58, 1.03)	0.153	-1.65 (-7.72, 4.42)	0.593		
Education, y	-0.24 (-0.63, 0.16)	0.243			0.08 (-0.61, 0.77)	0.823		
Total MMSE	-0.16 (-0.50, 0.17)	0.333			-0.50 (-1.71, 0.72)	0.419		
Caregiver								
Age, y	0.06 (-0.08, 0.20)	0.389			-0.06 (-0.26, 0.15)	0.600		
Sex (male)	3.84 (-0.02, 7.70)	0.051	3.55 (-0.38, 7.48)	0.077	-5.32 (-11.99, 1.35)	0.117	-5.37 (-12.00, 1.26)	0.112
Education, y	0.11 (-0.29, 0.51)	0.599			0.03 (-0.49, 0.55)	0.902		
Lives with patients	3.81 (0.11, 7.51)	0.044	3.42 (-0.40, 7.23)	0.079	-1.59 (-8.50, 5.32)	0.651		
NPI-D								
Hyperactivity	-0.20 (-0.60, 0.20)	0.322			0.73 (-0.36, 1.83)	0.187	-0.71 (-2.36, 0.94)	0.396
Psychosis	-0.27 (-0.70, 0.15)	0.212			0.10 (-2.02, 2.22)	0.924		
Affective	0.00 (-0.77, 0.77)	0.999			0.20 (-1.55, 1.94)	0.826		
Apathy	-0.13 (-0.80, 0.54)	0.700			2.36 (0.44, 4.29)	0.016	3.24 (0.31, 6.18)	0.031
CAS, min/d								
Communicating	0.01 (0.00, 0.02)	0.174			-0.02 (-0.06, 0.03)	0.491		
Transportation	-0.01 (-0.04, 0.01)	0.376			-0.05 (-0.13, 0.04)	0.292		
Dressing	0.00 (-0.07, 0.07)	0.965			0.09 (-0.18, 0.37)	0.514		
Eating	0.03 (-0.01, 0.06)	0.126	0.03 (0.00, 0.06)	0.110	0.07 (-0.09, 0.23)	0.380		
Grooming	0.01 (-0.05, 0.06)	0.846			0.02 (-0.26, 0.31)	0.883		
Supervision	0.00 (0.00, 0.01)	0.254			-0.01 (-0.17, 0.15)	0.923		

Bold type indicates statistical significance.

AD = Alzheimer's disease; CAS = Caregiver Activity Survey; CI = confidence interval; MCI = mild cognitive impairment; MMSE = mini-mental state examination; NPI-D = Neuropsychiatric Inventory Caregiver Distress Scale.

^aAnalyzed by backward elimination for multiple linear regression.

consumers. Therefore, the stated WTP of caregivers should be regarded as preferences for improved insurance coverage in the case of curative medications. Our study results suggested possible caregiver reactions to drug costs and could be considered as important reference on the value of AD medications in Taiwan.

This study has several limitations. First, while acquiring WTP values from informal caregivers, we did not include scenarios with adverse effects after taking the medication, so we do not know how payment support might differ in the face of probable adverse effect occurrence. Besides, we specified the probability of obtaining an overly positive health outcome after receiving a hypothetical treatment. The stated payments of caregivers may thus be overestimates of the true WTP. As AD is not currently curable, interventions have focused on delaying disease progression and reducing the negative impact of caregiving. Therefore, future WTP survey of AD medications should consider including different efficacy (eg, medications that cure AD and medications that stabilize AD) into the scenarios.¹⁵ In addition, whether informal caregivers understand the clinical course and prognosis of neurocognitive disorders is essential for them to decide the cost they are willing to pay. We only collected information from the patients and their caregivers, but did not provide detailed introduction of dementia and MCI to the caregivers before the interview. Second, our study design was cross-sectional, which precluded an observation of changes in WTP over time. Third, overestimation of WTP resulted from the "warm glow" affect should be expected, especially when respondents use WTP to express general approval for the treatment in questions.³⁹ However, by having to express WTP as a share of monthly income in our study, caregivers were prevented from overstating WTP values. Fourth, we did not acquire the cost that caregivers have already spent in caring the patients. This factor would influence their out-of-pocket WTP. Last, we used CAS to

measure the time spent by the caregivers in caring patients only during weekdays. However, caring time in the weekends has a great influence on quality of life of caregivers, and it has been shown that the leisure time of caregivers is more affected on weekends than on weekdays.⁴⁰ Future studies should include the time of caregivers' activity on weekends and weekdays, and to investigate whether caring time in different time periods would affect caregivers' WTP.

We investigated caregivers' out-of-pocket WTP for a hypothetical curative AD medication. Support for payment was significantly related to caregiver's income. The results could be considered as important guidance for policymaking on the insurance coverage of future AD medication in Taiwan.

ACKNOWLEDGMENTS

The work was supported by the Academia Sinica of Taiwan (AS-BD-108-2), the Ministry of Science and Technology of Taiwan (107-2321-B-075-001-, 107-2221-E-075-006-, 108-2321-B-075-001), Taipei Veterans General Hospital (V109C-061, VGHUST109-V1-5-1, V108D43-002-MY2-2), and the Brain Research Center, National Yang Ming Chiao Tung University from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

REFERENCES

1. Alzheimer's A. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement* 2016; 12:459–509.
2. Zucchella C, Bartolo M, Pasotti C, Chiappella L, Sinforiani E. Caregiver burden and coping in early-stage Alzheimer disease. *Alzheimer Dis Assoc Disord* 2012;26:55–60.

3. Mausbach BT, Chattillion EA, Roepke SK, Patterson TL, Grant I. A comparison of psychosocial outcomes in elderly Alzheimer caregivers and noncaregivers. *Am J Geriatr Psychiatry* 2013;21:5–13.
4. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med* 2008;148:379–97.
5. Wimo A, Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, et al; Donepezil Nordic Study Group. An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial. *Dement Geriatr Cogn Disord* 2003;15:44–54.
6. Feldman H, Gauthier S, Hecker J, Vellas B, Emir B, Mastey V, et al; Donepezil MSAD Study Investigators Group. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. *J Am Geriatr Soc* 2003;51:737–44.
7. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. *Am J Psychiatry* 2004;161:532–8.
8. Fuh JL, Wang SJ. Cost-effectiveness analysis of donepezil for mild to moderate Alzheimer's disease in Taiwan. *Int J Geriatr Psychiatry* 2008;23:73–8.
9. Huang LK, Chao SP, Hu CJ. Clinical trials of new drugs for Alzheimer disease. *J Biomed Sci* 2020;27:18.
10. Winblad B, Wimo A. Assessing the societal impact of acetylcholinesterase inhibitor therapies. *Alzheimer Dis Assoc Disord* 1999;13 (Suppl 2):S9–19.
11. Bala MV, Mausekopf JA, Wood LL. Willingness to pay as a measure of health benefits. *Pharmacoeconomics* 1999;15:9–18.
12. Diener A, O'Brien B, Gafni A. Health care contingent valuation studies: a review and classification of the literature. *Health Econ* 1998;7:313–26.
13. Mitchell RC, Carson RT. *Using Surveys to Value Public Goods: the Contingent Valuation Method*. 1st ed. Washington, DC: RFF Press; 1989.
14. Gafni A. Willingness-to-pay as a measure of benefits. Relevant questions in the context of public decisionmaking about health care programs. *Med Care* 1991;29:1246–52.
15. König M, Wettstein A. Caring for relatives with dementia: willingness-to-pay for a reduction in caregiver's burden. *Expert Rev Pharmacoecon Outcomes Res* 2002;2:535–47.
16. Wu G, Lanctôt KL, Herrmann N, Moosa S, Oh PI. The cost-benefit of cholinesterase inhibitors in mild to moderate dementia: a willingness-to-pay approach. *CNS Drugs* 2003;17:1045–57.
17. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
18. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183–94.
19. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308–14.
20. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the neuropsychiatric inventory caregiver distress scale. *J Am Geriatr Soc* 1998;46:210–5.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
22. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412–4.
23. Davis KL, Marin DB, Kane R, Patrick D, Peskind ER, Raskind MA, et al. The caregiver activity survey (CAS): development and validation of a new measure for caregivers of persons with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997;12:978–88.
24. Klose T. The contingent valuation method in health care. *Health Policy* 1999; 47:97–123.
25. van den Berg B, Bleichrodt H, Eeckhoudt L. The economic value of informal care: a study of informal caregivers' and patients' willingness to pay and willingness to accept for informal care. *Health Econ* 2005;14:363–76.
26. Blumenschein K, Johannesson M, Yokoyama KK, Freeman PR. Hypothetical versus real willingness to pay in the health care sector: results from a field experiment. *J Health Econ* 2001;20:441–57.
27. Nanyonjo A, Bagorogoza B, Kasteng F, Ayebale G, Makumbi F, Tomson G, et al; inSCALE Study Group. Estimating the cost of referral and willingness to pay for referral to higher-level health facilities: a case series study from an integrated community case management programme in Uganda. *BMC Health Serv Res* 2015;15:347.
28. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Ann Intern Med* 1993;118:201–10.
29. Aalten P, Verhey FR, Boziki M, Brugnolo A, Bullock R, Byrne EJ, et al. Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II. *Dement Geriatr Cogn Disord* 2008;25:1–8.
30. Bartlett R, Gjernes T, Lotherington AT, Obstfelder A. Gender, citizenship and dementia care: a scoping review of studies to inform policy and future research. *Health Soc Care Community* 2018;26:14–26.
31. Sharma N, Chakrabarti S, Grover S. Gender differences in caregiving among family - caregivers of people with mental illnesses. *World J Psychiatry* 2016;6:7–17.
32. Oremus M, Tarride JE, Pullenayegum E, Clayton N, Mugford G, Godwin M, et al; Canadian Willingness-To-Pay Study Group. Caregivers' willingness-to-pay for Alzheimer's disease medications in Canada. *Dementia (London)* 2015;14:63–79.
33. Lim YM, Son GR, Song JA, Beattie E. Factors affecting burden of family caregivers of community-dwelling ambulatory elders with dementia in Korea. *Arch Psychiatr Nurs* 2008;22:226–34.
34. Terum TM, Andersen JR, Rongve A, Aarsland D, Svendsboe EJ, Testad I. The relationship of specific items on the neuropsychiatric inventory to caregiver burden in dementia: a systematic review. *Int J Geriatr Psychiatry* 2017;32:703–17.
35. Jutkowitz E, Scerpella D, Pizzi LT, Marx K, Samus Q, Piersol CV, et al. Dementia family caregivers' willingness to pay for an In-home program to reduce behavioral symptoms and caregiver stress. *Pharmacoeconomics* 2019;37:563–72.
36. Gustavsson A, Jönsson L, McShane R, Boada M, Wimo A, Zbrozek AS. Willingness-to-pay for reductions in care need: estimating the value of informal care in Alzheimer's disease. *Int J Geriatr Psychiatry* 2010;25:622–32.
37. Zahodne LB, Tremont G. Unique effects of apathy and depression signs on cognition and function in amnesic mild cognitive impairment. *Int J Geriatr Psychiatry* 2013;28:50–6.
38. Appel LJ, Steinberg EP, Powe NR, Anderson GF, Dwyer SA, Faden RR. Risk reduction from low osmolality contrast media. What do patients think it is worth? *Med Care* 1990;28:324–37.
39. Andreoni J. Warm-glow versus cold-prickle: the effects of positive and negative framing on cooperation in experiments. *Quart J Econ* 1995; 110:1–21.
40. Rokicka M, Zajkowska O. Informal elderly caregiving and time spent on leisure: evidence from time use survey introduction and motivation. *Ageing Int* 2020; 45:393–410.