Co-Use of Donepezil and Hypnotics Among Alzheimer's Disease Patients Living in the Community

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Background: In clinical trials, sleep problems have been identified as side effects of donepezil, an acetylcholinesterase (AChE)-inhibiting medication for the treatment of Alzheimer's disease (AD). Poor sleep quality can exacerbate behavior problems among patients and add to the burden experienced by their caregivers. We examined the relationship between co-use of donepezil and hypnotics in a large sample of persons with AD living in the community.

Method: This secondary data analysis used cross-sectional subjects from a multiwave, consumer-based survey of AD caregivers conducted in 1997 and 1998. Rates of hypnotic use among users and non-users of donepezil were compared using chi-square analysis for independent samples, and multivariate logistic regression was used to identify significant independent correlates of hypnotic use.

Results: A total of 2638 caregivers completed at least 1 study wave. Use of hypnotics was higher in the donepezil subgroup (9.78%) compared with subjects not taking this medication (3.93%). Multivariate analysis demonstrated that donepezil use was independently linked to increased hypnotic use after controlling for the potential confounding effects of disruptive behavior and depressive symptoms (adjusted odds ratio = 3.34, $p < .001$).

Conclusion: In this large community sample, donepezil use was statistically linked to increased hypnotic use. Because sleep quality may be a critical issue for persons with AD and their caregivers, more rigorous evaluation of sleep problems linked to AChE-inhibitor treatment is indicated.

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In clinical trials, sleep problems, including insomnia and nightmares, have been identified as side effects of donepezil, an acetylcholinesterase (AChE)-inhibiting medication used for treatment of cognitive problems in Alzheimer's disease (AD). These side effects may be of concern because impaired sleep may exacerbate behavior problems among people with AD and add to the burden experienced by caregivers whose own sleep now may be disrupted.[1] Furthermore, sleep problems, as well as the medications used to treat sleep problems, add to the risk of serious falls and other injuries.[2,3]

Two of the 3 pivotal placebo-controlled clinical trials of donepezil have shown a statistically elevated incidence of insomnia in drug-treated subjects.[4–6] Rates of insomnia among placebo, 5-mg donepezil, and 10-mg donepezil groups were 5%, 8%, and 18%, respectively, in a 15-week U.S. study[4] and 4%, 7%, and 8% in an international trial.[6] In addition, according to the donepezil package insert, 9% of donepezil-treated patients reported insomnia compared to 6% for patients treated with placebo. A published letter described the case histories of 2 patients with probable AD who had frequent awakening and nightmares that were related to treatment with 5 mg of donepezil given at bedtime.[7] These problems, however, were resolved by switching to a morning dose. Moreover, a 12-week, randomized, open-label study comparing donepezil (up to 10 mg) and rivastigmine (up to 12 mg) found that the treatment-emergent incidence of abnormal dreams was higher with donepezil (7.1% versus 1.8%, respectively).[8]

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Patients participating in pivotal clinical trials of other AChE inhibitors, such as tacrine, rivastigmine, and galantamine, have not reported increased insomnia during adverse event reporting.[9–16] In addition, a 3-month, randomized, placebo-controlled trial showed that galantamine did not compromise sleep quality,[17] when sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI), a well-recognized questionnaire to measure sleep problems.[18] Also, in a sample of 6 AD patients that received treatment with rivastigmine for 12 weeks, the mean PSQI score improved from baseline, although statistical tests were not conducted due to the small sample size.[19]

There are several limitations in the studies that have examined the relationship between AChE-inhibiting medications and sleep quality. First, few studies utilize systematic assessments of sleep quality,[17,19] and more robust physiologic measurement involving polysomnography and/or actigraphy has been limited to minimal drug dosages far below the therapeutic range.[20] Instead, most assessments are based on reporting of adverse events during clinical trials, a method that consists of verbatim descriptions by physicians of medical symptoms and problems elicited from subjects and their caregivers in response to global inquiries on well-being. Second, clinical trials have limited generalizability.[21,22] Vulnerability to sleep problems may be higher among less selective AD patient populations, because patients with many serious comorbid conditions (for example, Parkinson's disease, major depression, and diabetes) are excluded from trials. Third, other data addressing sleep issues are limited to uncontrolled and case studies with few subjects.[7]

This study contributes to the literature on the relationship between donepezil use and possible sleep problems by examining treatment with donepezil, as well as other AChE inhibitors, and concomitant use of sedative-hypnotic prescription drugs in large, diverse cohorts of persons with AD living in the community. Information was based on caregiver reports but not subject to the inclusion and exclusion criteria common to clinical trials. The effectiveness of AChE inhibitors was not addressed in this analysis.

At the time of the study, most persons taking AChE inhibitors were treated with donepezil, which received approval by the U.S. Food and Drug Administration (FDA) in 1996. Although tacrine received FDA approval in 1994, its utilization has been limited by the risk of hepatotoxicity. Both rivastigmine and galantamine were not yet approved (approvals in 1999 and 2001, respectively).[23]

METHOD

Sample

The data were from the Alzheimer's Disease Caregiver Project, a large, multiwave, consumer-based mail survey of informal caregivers of people with AD across the United States. The purpose of the Alzheimer's Disease Caregiver Project, conducted by a proprietary health research company, was to obtain a profile of health status, functioning, medical utilization patterns, and health care costs of persons with AD and their family caregivers. In addition, a panel of clinical experts assisted in the development of the data collection instrument. Based on prior identification in a nationwide questionnaire, the sampling frame consisted of individuals who described themselves as caregivers for a person with AD. Separate lists of caregivers were used to sample caregivers at different waves, although a limited group of caregivers agreed to participate in subsequent surveys and thus provided follow-up information.

For this secondary data analysis, the total sample consisted of subjects from Wave 1 only (Wave 1 subjects), subjects from Wave 3 only (Wave 3 subjects), and subjects who participated at both waves (Multiwave subjects). Waves 1 and 3 were fielded in April 1997 and June 1998, respectively. Data from Wave 2 were not available for this analysis. The response rate for subjects by wave of initial contact was 11% in Wave 1 and 13% in Wave 3, with additional details on these samples published elsewhere.[24,25] We excluded caregivers of individuals who resided in nursing homes because prescribing practices for medication use among these residents may be subject to institutional practices.

To be included in the sample, subjects had to have complete data for both donepezil and hypnotic use. For Multiwave subjects, we maximized the incidence of co-use (of donepezil and a hypnotic) by reviewing both waves and selecting the wave with co-use. If no co-use was found, then the first wave with complete data was used.

Measures

Concurrent use was defined as current use of hypnotics and donepezil during the same wave of data collection. All data were based on caregiver report. The query on drug use included a list of brand name drugs (with generic names in parentheses) preceded by this introductory statement: "The following is a list of drugs sometimes used with AD patients. Please indicate which medications the person you are caring for uses today or has used in the past."

Hypnotic use was limited to current use of zolpidem tartrate and/or temazepam since the survey list included only these 2 prescription hypnotics. As previously described, Multiwave subjects were classified as concurrent medication users if they reported current donepezil and hypnotic use at either wave. At Wave 3, there were also queries on number of months using each drug. When duration of use was available, we excluded subjects whose use of hypnotics started prior to donepezil.

AD symptom levels, assessed by the 3 subscales from the Revised Memory and Behavior Problems Checklist (RMBPC),[26] addressed the frequency of behavior prob-

Table 1. Summary Statistics for Key Study Variables for Patients With Alzheimer's Disease (AD) and Their Caregivers

Variable	Wave 1[a] N[c]	Wave 1[a] Mean ± SD or Percentage	Wave 3[a] N[c]	Wave 3[a] Mean ± SD or Percentage	Multiwave[b] N[c]	Multiwave[b] Mean ± SD or Percentage
Demographics						
Patient						
Age, y	1108	78.09 ± 8.99	940	77.80 ± 8.92	545	76.38 ± 9.18
Gender	1111					
Male	415	37.35%	308	34.07%	216	39.56%
Female	696	62.65%	596	65.93%	330	60.44%
Caregiver (CG)						
Age, y	1076	56.60 ± 14.15	356	58.24 ± 11.90	529	58.99 ± 13.04
Gender	1079					
Male	239	22.15%	192	21.26%	101	19.09%
Female	840	77.85%	711	78.74%	428	80.91%
CG relationship to patient						
Spouse	382	34.51%	285	31.74%	250	46.04%
Child	593	53.57%	363	40.42%	252	46.41%
Other	132	11.92%	250	27.84%	41	7.55%
Patient AD symptoms[d]						
Disruptive behavior	1083	1.28 ± 0.91	949	1.13 ± 0.87	531	1.08 ± 0.80
Depression	1079	1.41 ± 0.95	944	1.28 ± 0.88	532	1.31 ± 0.89
Memory	1083	3.07 ± 0.95	948	3.12 ± 0.93	527	3.06 ± 0.91

[a]Includes all subjects who did not participate in multiple waves.
[b]The Multiwave sample is independent of subjects in Waves 1 and 3.
[c]Number of subjects will vary across variables due to missing data.
[d]Revised Memory and Behavior Problems Checklist subscale scores range from 0 (reflecting absence of all memory/behavior problems) to 4 (reflecting presence of all memory/behavior problems).

lems, depressive symptoms, and memory deficits. Having a theoretical range from 0 to 4, these subscale scores were derived by computing the mean of relevant items. Additional variables included the age and gender of the person with AD and their caregiver, and the caregiver's relationship to the person with AD.

Statistical Plan

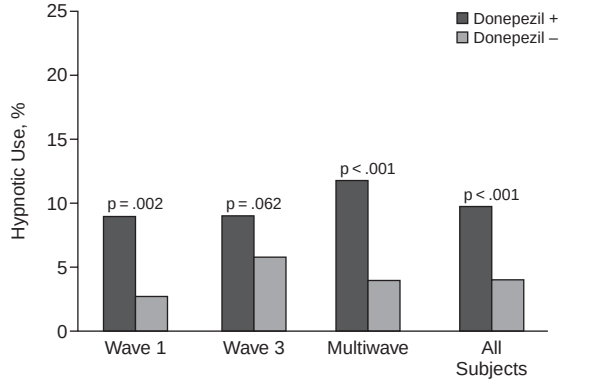
Comparisons were conducted within Waves 1 and 3, for the Multiwave subgroup, and for all respondents combined. Percentage distributions and means with standard deviations were used to describe the sample and subsamples on medication use, demographics, AD symptom scales, and caregiver relationship to the person with AD. Rates of hypnotic use among users and nonusers of donepezil were compared using chi-square analysis for independent samples. We also computed the odds ratios (ORs) linked to the use of hypnotics for all independent variables. Finally, we performed multivariate logistic analysis to examine the effect of AChE-inhibiting medications on hypnotic use, while controlling for other potentially confounding variables. Statistical significance was defined as a p value of less than or equal to .05 (2-tailed), with no correction for multiple tests.

RESULTS

In the total sample consisting of 2638 caregivers of persons with AD, the distribution was 1112 respondents from Wave 1 only, 980 respondents from Wave 3 only, and 546 respondents who participated at both waves. For Waves 1 and 3, the cross-sectional response rates ranged from 11% to 13%. Table 1 provides descriptive statistics for patient and caregiver demographics and patient AD symptom/behavior scores. Across subsamples, the demographic profile on age and gender for people with AD and their caregivers was similar. For the sample as a whole, the mean (SD) age of people with AD was 77.63 years (9.03) and the proportion of males and females was 36.67% and 63.33%. Caregivers had a mean (SD) age of 57.54 years (13.51), and their gender distribution was 21.19% male and 78.81% female. Across subsamples, the demographic profile on age and gender for people with AD and their caregivers was similar. Levels of AD symptoms, as reflected by behavior, depression, and memory subscale scores, also were consistent across subsamples. For the sample as a whole, the distribution on relationship type was 35.99% spouses, 47.41% children, and 16.60% other.

In all study participants, the rate of hypnotic use was 5.04%. The overall rates of treatment with AChE inhibitors including donepezil, tacrine, and rivastigmine were 18.99%, 4.69%, and 0.70%, respectively. In Wave 1, Wave 3, and the Multiwave participants, rates of hypnotic use were 3.15%, 6.63%, and 6.04%, respectively. The distribution of donepezil treatment by cohort was 78 donepezil users and 1034 nonusers in Wave 1, 278 donepezil users and 702 nonusers in Wave 3, and 145 donepezil users and 401 nonusers in the Multiwave cohort. Thus, from Wave 1 to Wave 3, rates of donepezil use increased from 7.00% to 28.37% and, in addition, the rate was 26.56% in the Multiwave sample. Because donepezil was introduced just prior to Wave 1, the 4-fold increase in use at Wave 3 is

Figure 1. Unadjusted Rates of Hypnotic Use by Donepezil Status and Study Wave



consistent with increased sales. Rates of tacrine usage were unchanged between Waves 1 and 3 (about 3.90%), although a higher usage was reported in the longitudinal sample (8.30%). Rivastigmine use, elicited in Wave 3 only, was limited to 6 subjects (0.63%). Because the drug was not approved, this usage most likely occurred within the context of a trial.

Using data included in Wave 3 only, 24 subjects who took both donepezil and a hypnotic had information on the number of months they had used these drugs. Of these 24 subjects, 21 (87.50%) started donepezil prior to hypnotics. Based on study criteria, the 3 subjects who had started hypnotics prior to starting donepezil were dropped from the analysis.

As shown in Figure 1, among all study participants, there were significant differences in rates of hypnotic use between donepezil users and nonusers (9.78% and 3.93%, respectively, $p < .001$). Within subsamples, comparisons of hypnotic use between donepezil users and nonusers in Wave 1, Wave 3, and the Multiwave subjects were 8.97% vs. 2.71% ($p = .002$), 8.99% vs. 5.70% ($p = .062$), and 11.72% vs. 3.99% ($p < .001$).

In the sample as a whole, as shown in Table 2, the OR for use of a hypnotic among users and nonusers of donepezil was 2.65 with a 95% confidence interval (CI) of 1.84 to 3.82 ($p < .001$). In addition, the ORs for donepezil users and nonusers were significant or near significant in the 3 subsamples: 3.54 at Wave 1 (CI = 1.50 to 8.39, $p = .004$), 1.64 at Wave 3 (CI = 0.97 to 2.75, $p = .064$), and 3.20 for the Multiwave subjects (CI = 1.57 to 6.51, $p = .001$). In contrast, in the total sample and all subsamples, ORs for hypnotic use were not significant for those treated with tacrine or rivastigmine. Due to the small number of patients taking these medications, these negative findings need to be interpreted with caution.

Hypnotic use was not related to demographic characteristics of persons with AD or their caregivers, or the relationship of the caregiver to the person with AD. Across subsamples, level of disruptive symptoms was significantly related to hypnotic use, having an OR of 1.71 (CI = 1.43 to 2.04, $p < .001$) in the total sample. In addition, in the total sample, the depressive symptoms score was significantly related to hypnotic use (OR = 1.28; CI = 1.06 to 1.54, $p = .009$), while the measure of memory problems was not (OR = 1.19; CI = 0.97 to 1.47, $p = .10$).

The multivariate results indicate that donepezil use was statistically associated with increased hypnotic use after controlling for disruptive behavior and depressive symptoms (when entered). The adjusted ORs for donepezil use were 4.29 in Wave 1 (CI = 1.75 to 10.47, $p = .001$), 1.94 in Wave 3 (CI = 1.13 to 3.34, $p = .016$), 4.25 in Multiwave subjects (CI = 1.99 to 9.07, $p < .001$), and 3.34 among all subjects (CI = 2.28 to 4.90, $p < .001$). For the sample as a whole and in all subsamples, there was an additional significant relationship between disruptive behavior and hypnotic use; in contrast, depressive symptoms did not further explain hypnotic use. Multivariate analysis was not performed for other AChE inhibitors because p values were not at or near designated significance based on bivariate results. The small numbers of subjects taking AChE inhibitors other than donepezil limited the statistical power of any inferences based on these data.

DISCUSSION

In this study, there was a statistical relationship between taking donepezil and increased use of hypnotics. Although the research design precluded any conclusions about causation, the results were strengthened by replication within the study. In 3 independent samples, the relationship between hypnotic use and donepezil was found to be significant or near significant. Furthermore, the relationship between donepezil and hypnotic use remained significant in all subsamples, even when we statistically controlled for other dimensions that were related to hypnotic use, namely levels of disruptive behavior and depressive symptoms.

A possible explanation for these results is that donepezil status was related to the propensity to seek treatment for problems and thus individuals who opted to take donepezil were more likely to take hypnotics for sleep problems. The small numbers of subjects taking AChE inhibitors other than donepezil precluded statistical inferences based on these data.

One rationale for the increased use of hypnotics among persons treated with donepezil is that donepezil-treated patients experienced more insomnia than persons who were not donepezil-treated. This interpretation would be consistent with evidence from clinical trials that indicated that insomnia was more common among patients treated with donepezil than those given placebo.[4,6] Although these clinical trials indicate that insomnia was a problem, this

Table 2. Bivariate and Multivariate Correlates of Hypnotic Use in Patients With Alzheimer's Disease

	Wave 1			Wave 3			Multiwave			All Subjects		
Variable	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
AChE inhibitors												
Donepezil	3.54	(1.50, 8.39)	.004	1.64	(0.97, 2.75)	.064	3.20	(1.57, 6.51)	.001	2.65	(1.84, 3.82)	< .001
Tacrine	2.50	(0.74, 8.54)	.14	1.42	(0.42, 4.76)	.57	0.75	(0.17, 3.27)	.70	1.46	(0.69, 3.06)	.32
Rivastigmine	NA	NA	NA	3.37	(0.39, 29.33)	.27	NA	NA	NA	3.37	(0.39, 29.33)	.27
Demographics												
Patient												
Age	0.98	(0.94, 1.01)	.22	1.01	(0.98, 1.04)	.73	0.97	(0.94, 1.01)	.10	0.99	(0.97, 1.01)	.17
Gender	0.79	(0.40, 1.56)	.49	0.87	(0.51, 1.48)	.60	0.77	(0.38, 1.57)	.48	0.83	(0.58, 1.19)	.32
Caregiver (CG)												
Age	0.98	(0.96, 1.01)	.20	0.99	(0.96, 1.03)	.64	1.01	(0.98, 1.03)	.69	1.00	(0.98, 1.01)	.58
Gender	0.78	(0.36, 1.70)	.54	2.20	(0.99, 4.95)	.052	1.10	(0.43, 2.66)	.89	1.33	(0.83, 2.12)	.24
Patient AD symptoms[a]												
Disruptive behavior	2.13	(1.53, 2.96)	< .001	1.68	(1.29, 2.17)	< .001	1.60	(1.07, 2.40)	.02	1.71	(1.43, 2.04)	< .001
Depression	1.35	(0.96, 1.89)	.09	1.38	(1.05, 1.82)	.02	1.15	(0.77, 1.71)	.49	1.28	(1.06, 1.54)	.009
Memory	1.09	(0.75, 1.57)	.66	1.16	(0.86, 1.57)	.33	1.43	(0.89, 2.29)	.14	1.19	(0.97, 1.47)	.10
CG relationship to patient												
Spouse	1.34	(0.67, 2.69)	.41	0.69	(0.38, 1.25)	.22	1.77	(0.86, 3.66)	.12	1.09	(0.75, 1.57)	.66
Child	0.86	(0.44, 1.71)	.67	0.89	(0.52, 1.51)	.65	0.68	(0.32, 1.42)	.30	0.76	(0.53, 1.09)	.14
Final models (multivariate)[b]	Adjusted OR	95% CI	p Value	Adjusted OR	95% CI	p Value	Adjusted OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Donepezil	4.29	(1.75, 10.47)	.001	1.94	(1.13, 3.34)	.016	4.25	(1.99, 9.07)	< .001	3.34	(2.28, 4.90)	< .001
Disruptive behavior	2.19	(1.56, 3.07)	< .001	1.68	(1.25, 2.28)	< .001	1.80	(1.18, 2.76)	.007	1.84	(1.50, 2.27)	< .001
Depression	NA	NA	NA	1.07	(0.78, 1.47)	.66	NA	NA	NA	0.99	(0.79, 1.22)	.89

[a]Revised Memory and Behavior Problems Checklist subscales.
[b]Limited to significant and near significant correlates of hypnotic use.
Abbreviations: AChE = acetylcholinesterase, AD = Alzheimer's disease, CI = confidence interval, OR = odds ratio.

condition occurred in only a small percentage of donepezil-treated patients.

Cholinergic pathways are thought to play an important role in sleep quality and, in particular, the onset and duration of rapid eye movement (REM) or dreaming sleep. Consequently, decreased cholinergic activity has been proposed as an explanation for the poorer quality sleep associated with normal aging, whereas cholinergic deterioration and dysregulation have been linked to the disruptive sleep problems found among individuals with AD, Parkinson's disease, and dementia with Lewy bodies.[27,28] Studies using polysomnography have demonstrated decreased REM sleep duration and decreased sleep efficiency (time asleep/time in bed) among individuals with AD relative to normal older adults.[29–31]

The adverse sleep effects linked to donepezil treatment[4,6] may be related to drug dosage, timing of administration, metabolism rates, or the difference in the mechanism of action of donepezil relative to other AChE-inhibiting medications.[32] Increased rates of insomnia and nightmares have not been reported in clinical trials with galantamine and rivastigmine.[9,13–16]

Currently, the impact of AChE-inhibiting medications on sleep quality is not well understood. Because AChE-inhibiting medications increase cortical levels of acetylcholine, there is speculation that they could play a role in normalizing sleep patterns among patients with REM sleep disorders and dementia.[19,28,33,34] However, use of cholinomimetic agents can produce paradoxical effects. For example, injections of physostigmine, an AChE inhibitor, have been shown to induce REM sleep or promote wakefulness depending on the dose used and timing.[35,36] Moreover, in one study, while REM sleep was induced by use of a cholinergic (muscarinic) agonist, subjects also experienced decreased slow wave sleep, suggesting that sleep quality and efficiency were disrupted by cholinergic stimulation.[37]

The survey results revealed a clear relationship between disruptive behavior problems, as measured by the RMBPC, and hypnotic use. Possible explanations include: (1) sleep problems and disruptive behavior in AD are triggered by a common deficit; (2) lack of sleep triggers disruptive behavior; (3) hypnotic use contributes to disruptive behavior; and (4) disruptive behavior is being treated by hypnotics. Since no information is available on the temporal sequencing of these events, we cannot

rule out the possibility that hypnotic use is affecting disruptive behavior. Other researchers have described an association between sleep problems, hypnotic use, and disruptive behavior, although the basis for this relationship is still very speculative.[1,38]

These results appear to contradict a prior study conducted by different researchers that also utilized data from the Alzheimer's Disease Caregiver Project.[25] These investigators found lower rates of sedative-hypnotic use in respondents who were treated with donepezil compared with those who were not. The prior study was based on a subsample of Wave 1 that did not reflect the experience of the complete sample. For example, donepezil subjects were limited to respondents who reported donepezil use in Waves 1 and 2, surveys conducted 6 months apart. This requirement excluded individuals who may have had problems with the drug and discontinued use prior to Wave 2. Similarly, comparison subjects were limited to individuals who reported use of at least 1 prescription drug in Wave 1. This requirement may have increased hypnotic use in the comparison group in Wave 2 because the medications identified in the survey were disproportionately psychotropic medications. Our findings in subjects who participated in Wave 1 were consistent with results in the independent panel of subjects who participated in Wave 3.

Several methodological limitations need to be considered in interpreting these results. First, hypnotic use was used as a proxy for insomnia because the survey had no specific measure of sleep problems. However, since these agents have no other indication, it is likely that use of hypnotics reflected problems with sleep. Second, individuals taking other AChE inhibitors (tacrine, rivastigmine) were grouped with those subjects who were not taking donepezil. This was a conservative strategy since any increased sleep problems among these individuals could precipitate the use of hypnotics among those not taking donepezil, making it more difficult to identify statistically significant differences between groups. Third, the sequencing of medication use cannot be established for all subjects. Thus, hypnotic use may have preceded donepezil use in some subjects. Nevertheless, at Wave 3, when limited data were available on the duration of medication use, the large majority (88%) of subjects who reported concurrent hypnotic and donepezil use started to use hypnotics the same month or after they started donepezil. Fourth, use of medications for sleep problems was limited to 2 hypnotic drugs. Although the study may underestimate the use of prescription medications for sleep problems, it is unlikely that underestimation was different among donepezil- and non–donepezil-treated subjects. Finally, this study was based on geographically diverse samples of convenience with low response rates despite large subject numbers.

Increased rates of hypnotic use among donepezil-treated survey participants offer indirect evidence that donepezil could be linked to increased sleep problems. Because sleep problems among AD patients can exacerbate inappropriate use of hypnotic agents, add to the distress of caregivers, and increase sleep problems among caregivers, the relationship between donepezil use and sleep problems warrants further investigation using more rigorous research designs and more comprehensive measurement of sleep problems.

Drug names: donepezil (Aricept), galantamine (Reminyl), rivastigmine (Exelon), tacrine (Cognex), temazepam (Restoril), zolpidem (Ambien).

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