Sedative-Hypnotic Use of Diphenhydramine in a Rural, Older Adult, Community-Based Cohort

Effects on Cognition

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Objective: The authors sought to identify patterns and associations of prescription and over-the-counter sedative-hypnotic use in an older, rural, blue-collar, community-based cohort in southwestern Pennsylvania over 10 years. Methods: A group of 1,627 individuals age 65 and over were recruited and assessed during 1987–1989 and reassessed during approximately biennial waves. Data included sleep medications, demographics, depressive symptoms, sleep complaints, and cognitive functioning (Mini-Mental State Exam [MMSE]). Results: At Waves 1 through 5, the mean age of the cohort increased from 73.4 to 80.5 years. Use of prescription sedative-hypnotics (primarily benzodiazepines) increased from 1.8% to 3.1%, and over-the-counter sedative-hypnotic use (primarily diphenhydramine) increased from 0.4% to 7.6%. At Wave 5 (1996–1998), 8.17% of the sample reported using diphenhydramine as a sleep aid. After adjusting for age and sex, diphenhydramine use was associated with higher education and more depressive symptoms, the latter becoming nonsignificant after controlling for initial insomnia. MMSE became significantly associated with diphenhydramine use when 143 subjects with dementia were excluded from the analysis. Conclusion: As the cohort aged, prescription sedative-hypnotic use remained relatively stable, whereas over-the-counter sedative use, principally diphenhydramine, increased substantially. The association of this drug with cognitive impairment in persons without dementia highlights its potential for causing adverse reactions in older adults. (Am J Geriatr Psychiatry 2003; 11:205–213)
ditional conditions, such as pain. Some seek prescription sedative-hypnotics from their physicians, whereas others self-medicate with alcohol or over-the-counter sleep aids, with or without the knowledge of their physicians. Reasons for self-medication may include the higher cost of prescription medication, limited access to healthcare, beliefs in the superiority of “natural” products, suggestions from friends and family, and increased direct marketing of sleep aids to the public.

The use of prescription drugs for sleep has not increased over time in North America, despite heavy advertising and the introduction of new benzodiazepines and new non-benzodiazepine sedative-hypnotic drugs such as zolpidem and zaleplon. However, the use of nonprescription sleep aids, including antihistamines, valerian, melatonin, herbal remedies, and kava powder has increased over the last decade and now exceeds prescription hypnotic use in the United States.2 Elderly Canadian subjects responding to a survey of nonprescription drug sleep aids reported similar patterns of nonprescription drug use for sleep—alcohol, antihistamines such as dimenhydrinate and diphenhydramine, analgesics such as acetaminophen, aspirin, and codeine-containing products, and herbal products such as herbal teas, St. John’s wort, and melatonin.3 The more recent introduction of a variety of nonprescription analgesic/hypnotic combinations appears to have contributed to the increased use of nonprescription hypnotic drugs.2

In an ongoing, prospective, epidemiological study of a cohort drawn from a rural American community, we examined the use of prescription and over-the-counter sedative-hypnotic drugs over 10 years of follow-up. We hypothesized that the use of these drugs might be associated with depressive symptoms as well as cognitive impairment in these older adults. Observing that by far the most common sedative-hypnotic agent used was diphenhydramine; we focused our analyses on factors cross-sectionally associated with the use of this drug during the 1996–1998 period.

**MATERIALS AND METHODS**

**Study Site and Population**

Originally designed as a population-based dementia registry, the Monongahela Valley Independent Elders Survey (MoVIES) study is being conducted within the mid-Monongahela Valley area of southwestern Pennsylvania. Study procedures receive annual approval from the University of Pittsburgh Institutional Review Board; sampling and recruitment of the study cohort have previously been described in detail.4–6 Eligibility criteria for entry into the study cohort, between 1987 and 1989, included community residence (i.e., not already being in long-term care), age of 65 years or older, fluency in English, and at least a sixth-grade education; the latter two criteria were intended to facilitate interpretation of the neuropsychological (cognitive) tests used to screen for dementia. The total number of randomly selected participants who met eligibility criteria and consented to participate was 1,422. An additional 259 volunteer participants met the same entry criteria and brought the total cohort size to 1,681 at study entry (1987–1989).5 All participants underwent a screening interview at study entry, and a subset of them (see below) underwent a clinical assessment for dementia. All surviving participants were subsequently contacted for follow-up screening interviews at approximately 2-year intervals, in a series of data collection “waves.” Data reported in this article were collected from participants who survived and consented to participate in each data collection period, from Wave 1 (1987–1989) through Wave 5 (1996–1998).

**Screening**

After providing written informed consent, each subject underwent an in-home screening and risk-factor assessment interview. The interview include approximately 25 minutes of cognitive screening,7 including the Mini-Mental State Exam (MMSE)8 and other, more specific, tests of cognitive domains known to be affected in dementia. The test battery included (but was not limited to) the neuropsychological battery constituted by the NIA Consortium to Establish a Registry for Alzheimer’s Disease (CERAD).9 Subjects also responded to a previously described modified version (mCES-D)10 of the Center for Epidemiological Studies-Depression scale (CES-D).11 Briefly, in the mCES-D, the questions are asked in the second-person by a trained interviewer. All 20 original CES-D items are included, but rated (0: no, 1: yes) according to whether or not the subject experienced them “most of the time” (operationalized as “3 or more days”) during the previous week. Thus, the mCES-D score reflects the number of symptoms expe-
rienced on 3 or more days of the preceding week, the maximum possible score being 20. A history of prescription and nonprescription (over-the-counter) medication use was taken as part of the screening interview, with drug information being obtained both from self-report and from medication bottle labels. Subjects (and reliable informants, when applicable and available) were asked to report their use of medications as of the day of the assessment, using a 2-week frame of reference if necessary. Questions regarding sleep complaints included difficulty falling asleep at night (initial insomnia), difficulty staying asleep or sleep continuity disturbance (intermittent insomnia), or early-morning awakening (terminal insomnia).

On the basis of their screening cognitive test scores at study entry, subjects were classified as cognitively intact or impaired on the basis of the following operational criteria: scores at or below the 10th percentile of the sample on either the general mental status test (MMSE) and/or at least one test of memory and one test of another cognitive domain. These criteria have previously been shown to be sensitive and specific for dementia. During subsequent biennial follow-up waves of cognitive screening with identical measures, subjects whose decline in scores (from previous waves) was at the 95th percentile of the cohort and those whose scores had newly fallen to below “impaired” levels as defined above, were classified as “cognitively declined.” At each wave, subjects classified as either cognitively impaired or declined were asked to undergo a clinical (diagnostic) evaluation for dementia, described below. Also, a sample of cognitively intact subjects, matched for age, sex, and education with subjects diagnosed as “demented” (see below) was also selected at Wave 1 as a control group for clinical evaluation.

### Diagnosis of Dementia

The MoVIES clinical evaluation protocol followed the diagnostic protocols established by CERAD and the University of Pittsburgh Alzheimer’s Disease Research Center (ADRC). It included a standardized history, brief general physical and detailed neurological exams, mental status exam, an informant interview, and a standard laboratory panel (hematology, chemistry, serology). Clinical evaluations were carried out blind to subjects' screening cognitive scores. Dementia was diagnosed according to DSM-III-R criteria. Diagnostically evaluated subjects received a Clinical Dementia Rating (CDR) score according to the CERAD protocol. On the CDR scale, scores (stages) of 0, 0.5, 1, 2, and 3 indicate no dementia, possible/incipient dementia, mild, moderate, and severe dementia, respectively. For the current analyses, we categorized as “demented” all those with CDR scores ≥0.5.

### Categories of Drugs

Prescription drug data were initially classified within American Hospital Formulary System (AHFS) categories. Over-the-counter (nonprescription) drugs were classified according to therapeutic category. Benzodiazepines classified as sedatives were flurazepam, temazepam, triazolam, and estazolam. For the current analyses, we did not include other benzodiazepines (e.g., alprazolam and lorazepam), or antidepressant or antipsychotic drugs, that subjects may or may not have been using for sleep. Our rationale was that we did not have access to information regarding the indications for which the subjects’ physicians had prescribed these drugs.

### Statistical Methods

First, we examined the frequencies and proportions of those taking any sedative/hypnotic drugs at each wave. Observing that the active component of the vast majority of these drugs was diphenhydramine, we focused our attention on this agent. Preliminary analyses showed that diphenhydramine use increased dramatically at the most recent wave (Wave 5, 1996–1999), when it was present in high enough frequency to permit multivariate analysis. We therefore focused our subsequent analyses on diphenhydramine use at this wave.

At Wave 5 (N=845), we examined the difference between diphenhydramine users and non-users in their distributions of age, sex, education, mental status (MMSE) scores, and depressive symptom (mCES-D) scores, using Mann-Whitney tests (for continuous variables) and chi-square or Fisher’s exact test (for categorical variables). The distributions of MMSE scores and mCES-D scores were highly skewed, as would be expected in a largely healthy community sample. Therefore, in addition to treating them as continuous variables for analyses using nonparametric tests, we also categorized them using cutpoints at the 10th percentile of our sample (MMSE≤23) to identify the most cognitively impaired tenth of our sample; and the 90th per-


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percentile of the sample (“≥5 on the mCES-D”), to identify the most depressed tenth of our sample.

For multivariate analyses, logistic-regression models were applied to data from Wave 5 to examine the association between diphenhydramine use (dependent variable) and age, sex, education, MMSE, and mCES-D scores, and subjective sleep complaints (independent variables). In the first model, the independent variables were age, sex, education, original recruitment in random sample versus volunteer sample, MMSE score, and mCES-D score. In the second model, we added three insomnia complaints: initial, intermittent, and terminal insomnia. We excluded from these analyses 50 subjects who had incomplete data on one or more of the above variables, reducing the sample size to 795 for these analyses.

We then fit the above logistic regression-models again, excluding 143 subjects with dementia, defined as those with CDR≥0.5; in case these subjects had “bottomed out” on the MMSE and were not susceptible to further variation related to use of the drug. The sample size for this analysis was therefore 652.

Goodness of fit for the logistic-regression models was examined by use of the Hosmer-Lemeshow goodness-of-fit test. All the models indicated adequate fit.

RESULTS

A total of 1,681 subjects were enrolled at Wave 1 (baseline, study entry). Participants at subsequent waves numbered 1,342 (Wave 2), 1,165 (Wave 3), 1,016 (Wave 4), and 845 (Wave 5). Subjects with incomplete medication information were deleted from the sample for the present analyses; the total sample sizes used for this study at Waves 1 through 5 are, therefore, 1,627, 1,338, 1,164, 1,015 and 845. Mean (standard deviation [SD]) ages at each wave were 73.4 (5.9), 74.9 (5.5), 76.9 (5.3), 78.8 (5.1), and 80.5 (4.6) years, respectively.

Table 1 shows the number of subjects taking sedative-hypnotic drugs, within prescription and non-prescription (over-the-counter, OTC) categories at each wave. At these consecutive waves, use of prescription sedative-hypnotics (primarily benzodiazepines) was reported in 1.8%, 2.5%, 2.0%, 1.3%, and 3.1% of the samples, respectively, and OTC sedative-hypnotics (primarily diphenhydramine) were reported as used by 0.4%, 0.6%, 1.6%, 3.0%, and 7.6%, respectively (not in Table 1, which shows combined prescription and OTC diphenhydramine). The proportion of those taking sedative-hypnotic drugs increased at each consecutive wave, with a sharp increase in the most recent wave (2.2% at Wave 1 to 10.6% at Wave 5). This increase was mainly due to the increase in diphenhydramine use. At Wave 1, equal numbers (n = 6 each) of subjects were taking prescription and OTC diphenhydramine; by Wave 5, 12 and 57 subjects were taking prescription and OTC diphenhydramine.

At Wave 5, the cohort size was 845, representing attrition since Wave 4 of 13.6% from mortality, 2.7% due to permanent relocation and dropout, and 3.2% who skipped Wave 5 only. Of the 845, 657 were originally recruited from the random sample and 188 from the volunteer sample. The mean (SD) ages of diphenhydramine users and non-users were almost identical, at 80.1 (4.6) and 80.5 (4.6) years, respectively, not significantly different by Mann-Whitney test (p = 0.436; Table 2). Women comprised 73.9% of users and 64.2% of non-users, but these proportions were not significantly different by chi-square test (1 df; p = 0.104). Users were significantly better educated: those with greater than high school education comprised 62.5% of non-users and 76.8% of users, a significant difference by chi-square test (1 df; p = 0.018).

Of the 845, 25 did not complete the MMSE, and 26 had incomplete mCES-D data. The mean (SD) MMSE scores of all 820 subjects, of the diphenhydramine users, and the diphenhydramine non-users, were 26.6 (3.7), 26.5 (3.8), and 26.6 (3.7), respectively. No subjects with MMSE ≤18 were taking diphenhydramine.

Table 2 also shows the proportions of subjects with low MMSE scores (≤23), high mCES-D scores (≥5), and insomnia complaints: initial, intermittent, and terminal insomnia, among users and non-users of diphenhydramine. The table also summarizes the results of unadjusted and adjusted (multiple logistic regression) analyses of associations of these variables with diphenhydramine use. A diagnosis of dementia, with a CDR score ≥0.5, was received by 143 individuals. Their mean (SD) MMSE score was 23.7 (3.5), whereas that of the non-demented subjects was 27.7 (1.8).

The results of the four regression models are summarized in Table 2 as odds ratios (OR) with 95% confidence intervals (CI) and p values derived from Wald chi-square tests with 1 df. In Model I, including all subjects, and not including sleep complaints, higher education (OR: 2.2; p = 0.021) and higher depression scores (OR:
TABLE 1. Prescription and nonprescription sedative-hypnotic use over 10 years, n (%)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Diphenhydramine</td>
<td>12 (0.71)</td>
<td>15 (1.12)</td>
<td>22 (1.89)</td>
<td>34 (3.35)</td>
<td>69 (8.17)</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>4 (0.24)</td>
<td>5 (0.37)</td>
<td>4 (0.34)</td>
<td>1 (0.10)</td>
<td>—</td>
</tr>
<tr>
<td>Temazepam</td>
<td>6 (0.36)</td>
<td>7 (0.52)</td>
<td>9 (0.77)</td>
<td>5 (0.49)</td>
<td>3 (0.36)</td>
</tr>
<tr>
<td>Triazolam</td>
<td>8 (0.54)</td>
<td>10 (0.75)</td>
<td>—</td>
<td>—</td>
<td>1 (0.12)</td>
</tr>
<tr>
<td>Estazolam</td>
<td>—</td>
<td>—</td>
<td>2 (0.17)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Ethchlorvinyl</td>
<td>1 (0.06)</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>Barbiturates</td>
<td>4 (0.24)</td>
<td>6 (0.52)</td>
<td>4 (0.34)</td>
<td>1 (0.10)</td>
<td>1 (0.12)</td>
</tr>
<tr>
<td>Glutethimide</td>
<td>1 (0.06)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Zolpidem</td>
<td>—</td>
<td>—</td>
<td>2 (0.20)</td>
<td>10 (1.18)</td>
<td>—</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>—</td>
<td>—</td>
<td>1 (0.09)</td>
<td>4 (0.47)</td>
<td>—</td>
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<tr>
<td>Melatonin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (0.12)</td>
</tr>
<tr>
<td>Valerian</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (0.12)</td>
</tr>
<tr>
<td>Kava</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (0.12)</td>
</tr>
<tr>
<td>Total subjects</td>
<td>36 (2.20)</td>
<td>41 (3.06)</td>
<td>41 (3.52)</td>
<td>43 (4.23)</td>
<td>90 (10.65)</td>
</tr>
<tr>
<td>Total drugs</td>
<td>36</td>
<td>43</td>
<td>42</td>
<td>43</td>
<td>91</td>
</tr>
</tbody>
</table>

* Diphenhydramine-containing products include: generic diphenhydramine, Benadryl, Benylin, Nerveine, Aid-To-Sleep, Nytol, Robitussin PM, Tylenol PM, Motrin PM, acetaminophen PM, Excedrin PM, Legatrin PM.

** Total number of drugs exceeds total number of subjects when one or more subjects reports taking more than one drug.

<table>
<thead>
<tr>
<th>Unadjusted Analyses</th>
<th>Adjusted (multivariate) Analyses</th>
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<tbody>
<tr>
<td></td>
<td>All Subjects (N=795)</td>
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<tr>
<td></td>
<td>Model I, excluding insomnia complaints</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>80.1 (4.6)</td>
</tr>
<tr>
<td>% women</td>
<td>73.9</td>
</tr>
<tr>
<td>% from volunteer sample</td>
<td>26.1</td>
</tr>
<tr>
<td>% ≥high school graduate</td>
<td>76.8</td>
</tr>
<tr>
<td>% MMSE ≤23</td>
<td>n=65</td>
</tr>
<tr>
<td>% ≥5 depressive symptoms</td>
<td>n=66</td>
</tr>
<tr>
<td></td>
<td>n=15.2</td>
</tr>
<tr>
<td>Insomnia Complaints:</td>
<td>n=64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>% initial insomnia</td>
<td>59.4</td>
</tr>
<tr>
<td>% intermittent insomnia</td>
<td>51.6</td>
</tr>
<tr>
<td>% terminal insomnia</td>
<td>32.8</td>
</tr>
<tr>
<td>−2 log likelihood</td>
<td>n/a</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Note: CI: confidence interval; SD: standard deviation; MMSE: Mini-Mental State Exam.
<sup>a</sup>Based on chi-square test unless otherwise specified.
<sup>b</sup>Based on Mann-Whitney Test.
<sup>*</sup>Statistically significant at p<0.05 or less.
difficulty in falling asleep, whereas the association with depressive symptoms became non-significant. Thus, the initial insomnia related to depression was the likely basis of the relationship between depression and diphenhydramine use.

Our primary hypothesis was that the potential benefits of diphenhydramine as a sleep aid might be overridden by its negative consequences for cognitive functioning in these older adults. The cognitive effects of diphenhydramine in older persons are usually attributed to its anticholinergic properties. A role may also be played by interactions mediated by cytochrome oxidase enzyme–2D6 interactions, in which diphenhydramine may raise the anticholinergic effects of other drugs.

In our overall sample, our initial hypothesis was not confirmed. Although there was a twofold increased probability of a low general mental status (MMSE) score in diphenhydramine users, even after adjusting for the possible confounding effects of depression, the association was not statistically significant. However, when individuals with dementia were excluded from analysis, the association between the MMSE and diphenhydramine became much stronger and statistically significant. One possible interpretation is a floor effect, that is, that individuals with dementia had sufficient brain dysfunction that their background cognitive impairment was not substantially affected by diphenhydramine use. The explanation may also partly be that the 143 demented subjects included the 13 subjects with MMSE <18, none of whom were taking diphenhydramine.

Evidence from previous studies is mixed. We are not aware of any previous population-based studies on the relationship between cognitive functioning and chronic use of diphenhydramine or other anticholinergic drugs. Results are difficult to compare across studies because of variation in study population (most often patients or volunteers), subjects’ age, study design (observational or experimental), and the cognitive measures that were examined.

Previous studies of clinical samples have revealed clear associations of anticholinergic drug levels or anticholinergic activity with delirium or diminished cognitive/functional ability in surgical, medical, nursing home, and psychiatric (depressed) patients. Although diphenhydramine was found beneficial in one treatment study of non-cognitive behavioral disturbances in dementia, another report found that as low a single dose as 25 mg–50 mg of diphenhydramine caused delirium in mildly demented patients. A few studies have also suggested that anticholinergic drugs cause cognitive deficits in patients with Parkinson disease, a group for whom such drugs are frequently prescribed.

Experimental studies of diphenhydramine in healthy older adults have yielded mixed results with respect to cognitive impairment. In one study, detectable anticholinergic levels of commonly prescribed medications were associated with impairments in memory and attention in normal elderly subjects. In another study, older women appeared to suffer lesser impairments than younger adults. In studies of younger adults, diphenhydramine produced less consistent memory impairment than did scopolamine, but more sedation and cognitive deficits than the newer, less centrally-acting antihistamines. One study found that drowsiness and mental impairment had parallel slopes relative to diphenhydramine concentrations, although the drowsiness lasted longer.

Our study had some limitations. Medication use data were obtained by self-report from subjects/informants and bottle labels. We had no access to medical records or other sources of information regarding what the participants’ physicians may have prescribed and for which indications. However, the bulk of the reported diphenhydramine use in our study sample was purchased over the counter. Our data on drug use is presumed accurate as regards “regular” use as of the time of assessment at Wave 5; we have no objective data on actual frequency or duration of use, but only 8 of the 69 users at Wave 5 had reported being users at Wave 4. The number of users provided sufficient power for hypothesis-testing only at Wave 5. Thus, our analyses are cross-sectional in nature and do not permit the determination of the direction of the associations we have reported here. For example, we cannot state whether diphenhydramine use led to cognitive impairment or vice versa. Power may also have been insufficient to detect small effects because, in this population-based sample, the proportion of individuals with significant depressive symptoms and cognitive impairment was low. However, the population-based nature of the sample enhances its generalizability to the community at-large, since it is less affected by selection bias than samples of patients or volunteers on whom many previous studies were based.

Diphenhydramine use as a sleep aid is on the rise among older adults. Many users of nonprescription...
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sleep aids, and indeed many physicians, may be unaware that diphenhydramine is an ingredient of these products. Its potential adverse effects on cognition should be considered. Practitioners should be alert to their patients’ use of over-the-counter sleep aids, particularly when cognitive impairment is present.

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